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The use of allografts in knee reconstructions: systematic review and cost-effectiveness analysis

A report for the European Society of Sport Traumatology, Knee Surgery and Arthroscopy (ESSKA).

Authors (Warwick Medical School unless otherwise stated)

Norman Waugh, professor of public health medicine and health technology assessment

Hema Mistry, health economist

Emma Loveman, Effective Evidence, Waterlooville, Hampshire UK

Jill Colquitt, Effective Evidence, Waterlooville, Hampshire, UK (http://effectiveevidence.org)

Pamela Royle, information specialist

Nick A Smith, orthopaedic surgeon, University Hospitals Coventry and Warwickshire NHS Trust, Coventry UK.

Andrew Metcalfe, associate professor of orthopaedics and consultant orthopaedic surgeon, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK.

Correspondence Address:

Professor Norman Waugh, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry UK.

norman.waugh@warwick.ac.uk

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Additional Publications

Shortened versions of some sections have been published in the June 2019 issue of Knee Surgery, Sports Traumatology, Arthroscopy, which was a special issue on allografts.

Waugh N, Mistry H. A brief introduction to health economics. KSSTA 2019; 27:1704–1707 https://doi.org/10.1007/s00167-019-05372-y

Waugh N, Mistry H, Metcalfe A, Colquitt J, Loveman E, Royle P, Smith N. Allografts in reconstruction of the posterior cruciate ligament: a health economics perspective. KSSTA 2019; 27:1810–1816. https://doi.org/10.1007/s00167-019-05477-4

Mistry H, Metcalfe A, Smith N, Loveman E, Colquitt J, Royle P, Waugh N. The cost-effectiveness of osteochondral allograft transplantation in the knee. *KSSTA* 2019; 27:1739–1753 https://doi.org/10.1007/s00167-019-05392-8

Mistry H, Metcalfe A, Colquitt J, Loveman E, Smith N, Royle P, Waugh N. Autograft or allograft for reconstruction of anterior cruciate ligament: a health economics perspective. KSSTA 2019; 27:1782–1790 https://doi.org/10.1007/s00167-019-05436-z*KSSTA 2019*

Waugh N, Mistry H, Metcalfe A, Loveman E, Colquitt J, Royle P, Smith NA, Spalding T. Meniscal allograft transplantation after meniscectomy: clinical effectiveness and cost‑effectiveness. KSSTA 2019;27:1825–1839 https://doi.org/10.1007/s00167-019-05504-4

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Abbreviations

4SHS	four-strand hamstring
ACI	autologous chondrocyte implantation
ACL	anterior cruciate ligament
ACLR	anterior cruciate ligament reconstruction
ALB	anterolateral bundle
AM	anteromedially
BPTB	bone-patellar tendon-bone
CC	complication and comorbidity
CCT	controlled clinical trial
CD	cannot determine
CI	confidence interval
CKRS	Cincinnati Knee Rating System
DB	double bundle
DBPTB	double-layer bone–patellar tendon–bone
ESSKA	European Society for Sports Traumatology, Knee Surgery and Arthroscopy
FTD	full-thickness chondral defects
HR	hazard ratio
HS	hamstring
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IKDC	International Knee Documentation Committee
IQR	interquartile range
KL	Kellgren–Lawrence
KM	Kaplan-Meier
KOOS	Knee Injury and Osteoarthritis Outcome Score
KR	knee replacement
KSS	Knee Society Score
MARS	Multicenter ACL Revision Study
MAT	meniscal allograft transplantation
MCS	mental component summary
MOON	Multicenter Orthopaedic Outcomes Network
MOPS	Missouri Osteochondral Preservations System
MRI	magnetic resonance imaging
NA	not applicable
NAT	nucleic acid testing
ND	no chondral defect
NICE	National Institute for Health and Care Excellence

NIH	National Institute for Health
NR	not reported
OA	osteoarthritis
OAT	osteochondral autograft transplantation
OCA	osteochondral allografts
OCD	osteochondritis dissecans
PA	posteroanterior
PCL	posterior cruciate ligament
PCS	physical component summary
PKR	partial knee replacement
PL	posterolaterally
PMB	posteromedial bundle
PSS	personal social services
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RCT	randomised controlled trial
ROB	risk of bias
RR	risk ratio
SB	single bundle
SD	standard deviation
SE	standard error
TKA	total knee arthroplasty
TKR	total knee replacement
TOPKAT	Total or Partial Knee Arthroplasty Trial
UKA	unicompartmental knee arthroplasty
UKR	unicompartmental knee replacement
WMD	weighted mean difference
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Summary

Osteochondral allografts

Osteochondral allografts (OCA) consist of a layer of hyaline cartilage and a layer of underlying bone. They are used to repair combined defects of articular cartilage and bone, a situation where interventions such as autologous chondrocyte implantation (ACI) are unlikely to be successful. Such defects often occur in people far too young to have knee replacement, for whom the main alternative to OCA is conservative symptomatic care, which will not prevent development of osteoarthritis, though a load-reducing osteotomy may help to delay progression.

There is good evidence that osteochondral allografts are clinically effective with a high graft survival rate over 20 years. If an OCA graft fails, there is some evidence that revision with a second OCA is also effective, though less so than primary OCA.

OCA appears highly cost-effective, but the cost per quality adjusted life year varies according to the widely-varying costs of allografts. Based on one small study, revision OCA also appears very cost-effective.

There are marked differences in the provision of OCA across Europe. OCA is currently uncommon in the UK, but large OCAs are not available at all in many European countries. Spain is an exception.

The reasons for lack of availability of an effective and cost-effective treatment for osteochondral defects will be considered by ESSKA.

Allografts in reconstruction of the anterior cruciate ligament

Reconstruction of the anterior cruciate ligament (ACL) is highly successful whether with autografts or allografts. Autografts are nowadays most commonly from the hamstrings, but bone-patellar tendon-bone (BPTB) autografts may also be used.

Failures do occur but this does not necessarily mean that there was something wrong with the procedure or the technology. It should be borne in mind that people having these procedures do so because they have damaged or ruptured their own tissues, perhaps by putting great demands on the knee structures, often during sport.

Recent studies show little difference in failure rates between autografts and allografts (about 6% and 7% respectively). In cost-effectiveness analysis, the price differential is the main factor, making autografts the first choice.

However there will be situations, particularly in revision ACL reconstruction, where an allograft may be preferred, or may be the only reasonable option available.

Allografts in posterior cruciate ligament reconstruction

The available evidence does not show any significant difference in clinical effectiveness between autografts and allografts. Allografts are most costly. So if an autograft is available, and if there is no clinical reason to prefer an allograft, then on cost grounds, autografts should be preferred. However there will be situations where an allograft might be preferred.

Meniscal allografts.

This is the most difficult area. It is generally accepted that meniscectomy leads to osteoarthritis, but the speed of progression varies amongst studies. The damage to articular cartilage at the time of the meniscal injury is common, so it may sometimes be difficult to know how much of the osteoarthritis (OA) to attribute to meniscectomy. Meniscal damage without meniscectomy is associated with later OA. The prevalence of OA at any time period depends on how it is diagnosed (radiological, MRI, symptomatic).

The evidence on whether meniscal allograft transplantation (MAT) protects is more difficult. A systematic review by Smith and colleagues concluded that;

"*There is some evidence to support the hypothesis that meniscal allograft transplantation reduces the progression of osteoarthritis, although it is unlikely to be as effective as the native meniscus. If this is proven, there may be a role for prophylactic meniscal allograft transplantation in selected patients. Well-designed randomised controlled trials are needed to further test this hypothesis.*"

MAT relieves symptoms in those who have them after meniscectomy, and thereby improves quality of life. However the proportion of patients that would benefit significantly from MAT after meniscectomy is uncertain, even if cost was not a consideration. A proportion, perhaps 10-20% (others might suggest a higher figure) do particularly badly after meniscectomy. One small study even inserted MATs prophylactically at time of meniscectomy.

MAT is clinically effective in relieving symptoms, as measured by scores such as Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC), Lysholm and Tegner. However, most studies had no matched controls receiving conservative care, so the benefits of MAT over conservative care (including physiotherapy) cannot be quantified, making cost-effectiveness analysis problematic. It is not enough to say "MAT works". In cost-effectiveness analysis it is the effect size compared to the comparator that matters.

The extent to which MAT reduces or delays progression to advanced OA, is uncertain. If MAT reduced or delayed knee replacement, that would result in savings to offset the cost of MAT. A cost-effectiveness analysis by Bendich and colleagues estimated that MAT would need to reduce progression to severe OA by 31% to be cost-effective, in their base case of someone aged 30, BMI 20 and no OA. In other scenarios, a smaller reduction in progression would make MAT cost-effective. So given the current lack of evidence on chondroprotection, we cannot say that MAT is definitely cost-effective, but it is likely to be so in some groups. One high priority for research is for ways of identifying the 10-20% of people who do worst after meniscectomy.

Introduction

This health technology assessment (HTA) report was commissioned by ESSKA. The aim was to assess the cost-effectiveness of allografts for various indications in the knee.

HTA research addresses the following questions;

- Does it work?
- At what cost?
- Is it worth it, compared to other possible uses of funds?

This is done in order to help policy-makers with a fourth question: Should we provide it?

Underlying all of this is the hard reality that funds are always scarce, and that health services are never able to fund every treatment that might do some good for some people. So choices have to be made about what to fund and what not to fund.

The benefits of health care range from symptoms relieved to lives prolonged. We capture the various benefits through the common currency of the QALY – the quality adjusted life year – which captures both length of life and quality of life. So if an intervention reduces knee pain, that increases quality of life and the impact can be measured in QALYs. For example, if someone with a painful knee has a quality of life reduced by 20% - a "utility" reduction of 0.2 on a scale of 0 to 1.0 where 1.0 is perfect health – for 10 years, that is a loss of 2.0 QALYs. If an intervention restores utility to normal, we gain 2 QALYs. Based on the cost of the intervention and all other associated costs and savings, we can then estimate the cost per QALY. The total costings will include any savings, for example if knee replacement is avoided or postponed.

The cost per QALY that is considered affordable various amongst countries. In the UK, the National Institute for Health and Care Excellence (NICE) regards anything under £20,000 per QALY as acceptable, and will consider costs per QALY in the £20,000 to £30,000, depending on the strength of evidence. In some circumstances, NICE will accept a much higher cost per QALY, but so far, none of those are in orthopaedics. So for our patient with the 20% reduction in quality of life for 10 years, NICE would consider that an investment of £40,000 to £60,000 would be justified, even without considering possible future savings.

One issue that we have to take into account is discounting. This involves adjusting future costs and benefits to current values. It is based on the principle that £1000 or $1000 is valued more highly if received now, than in the future. The UK Government applies a 3.5% discount rate to future costs and benefits. So £1000 now is valued at £965 in one year's time. This has implications for interventions that lead to future costs avoided. For example, if a knee replacement costs £6,000 today, the discounted cost is £4201 at 10 years and £3516 at 15 years. So if intervention now leads to knee replacement avoided in 10 years, the savings are only assessed to be £4201. However, discounting can also support interventions that postpone knee replacements – if an intervention now postpones future knee replacement by 5 years, that equates to a saving of £4201 - £3516 = £658.

Other countries apply different discount rates and sometimes the rates differ for costs and outcomes, for example 6% for costs and 1.5% for benefits.

Discounting has been hotly debated, with some arguing that costs should be discounted but benefits not, but in practice decision making processes are based on discount rates set by governments.

In this report, we have used mostly UK costs for surgical procedures and other care. We have given details of cost items so that colleagues in other countries can consider the impact of using their own costs. We have also explained which factors are most important in the cost-effectiveness analysis.

Methods

Fuller details of methods are given later, but in brief;

- We searched the databases Ovid Medline, Ovid Embase, Web of Science and the Cochrane Library for articles published from the year 2000 until February 15th 2018. The Medline search strategy and the numbers of records obtained are shown in Appendix 1.
- Titles and abstracts of retrieved studies were screened by two people, with full papers obtained if inclusion or exclusion was uncertain from the abstract
- Standard systematic review methods were used with quality assessment of included studies using standard checklists for both reviews and primary studies, and checking of data extractions by a second reviewer
- Meta-analysis was done only if appropriate.

1. Osteochondral allografts

Summary

Osteochondral allografts consist of a layer of hyaline cartilage and a layer of underlying bone. They are used to repair combined defects of articular cartilage and bone, a situation where interventions such as autologous chondrocyte implantation (ACI) are unlikely to be successful. Such defects often occur in people far too young to have knee replacement, for whom the main alternative to osteochondral allografts (OCA) is conservative symptomatic care, which will not prevent development of osteoarthritis, though a load-reducing osteotomy may help to delay progression.

There is good evidence that osteochondral allografts are clinically effective with a high graft survival rate over 20 years. If an OCA graft fails, there is some evidence that revision with a second OCA is also effective, though less so than primary OCA.

OCA appears highly cost-effective, but the cost per quality adjusted life year varies according to the widely-varying costs of allografts. Based on one small study, revision OCA also appears very cost-effective.

There are marked differences in the provision of OCA across Europe. OCA is currently uncommon in the UK, but large OCAs are not available at all in many European countries. Spain is an exception.

The reasons for lack of availability of an effective and cost-effective treatment for osteochondral defects will be considered by ESSKA.

Background

Osteochondral allografts replace not only the articular cartilage but also a layer of underlying bone. The articular cartilage is the same thickness as the patient's own (about 4 mm), and the living chondrocytes are too embedded in the cartilage to trigger a significant immune response. The bone component in the allograft forms a scaffold into which host cells can move.[1] The allograft can therefore almost exactly replace the defect in the host's knee.

Options are limited for a patient with a defect in both the cartilage and the underlying bone (osteochondral defect), which may be due to trauma or osteochondritis dissecans (OCD). Rarer causes include corticosteroid induced osteonecrosis.[2] OCD occurring in a patient that has open bone growth plates is more likely to spontaneously heal, and if not attempts can be made to fix the loose osteochondral fragment in an attempt to reduce pain and stimulate healing. However this is not always successful and removal may be necessary. OCD occurring in patients with closed growth plates less commonly heals and is more likely to need fixation and possible subsequent failure. It has been shown in historical studies[3] [4] that patients with OCD, particularly ones where the fragment has been removed, have a very high risk of future osteoarthritis and poor knee function. Most of these patients, as well as those with traumatic lesions, are young and active, and knee arthroplasty is rarely indicated. A knee arthroplasty does not restore full knee function for most young patients. In older patient, a unicompartmental knee arthroplasty may offer slightly better rates of return to sporting activities[5], but knee arthroplasty rarely results in normal knee function, regardless of type. Knee arthroplasty, whether total or unicompartmental, is rarely performed in patients under 50 years of age. The full results of the TOPKAT trial comparing total and unicompartment arthroplasty

should be available shortly[6, 7]. A knee arthroplasty performed in a young patient will usually result in failure in their lifetime, resulting in the consequent need for further replacements, which become less successful each time. It was recently shown by Bayliss and colleagues[8] that the lifetime risk of revision for a total knee replacement was 35% for men and 20% for women having their primary procedure in their early 50's. Data on the risk of revision for patients younger than this is sparse as it is rarely performed, but the risk of revision is thought to be exponentially higher. This is partly due to increased activity as well as longer life expectancy.

Management of "deep OCD" has been a challenge. Apart from OCA, other options that have been tried include a morcellised bone graft in the base covered with an ACI patch (probably more expensive than OCA), and synthetic grafts. Osteochondral autograft transfer such as mosaicplasty can be used to treat osteochondral lesions but donor site morbidity limits this to small lesions. Cartilage restoration techniques such as microfracture and autologous chondrocyte implantation (ACI) do not replace bone defects and do not do well when underlying bone is damaged. Some symptoms may be relieved by an unloading osteotomy[9] but this does not resolve the underlying intra-articular damage.

McCulloch and colleagues[9] have set out the advantages of OCA: the ability to repair larger and deeper defects with mature hyaline cartilage, to resolve the underlying bone defect, and to do so in a single procedure. Briggs and colleagues[10] note that in the past, OCA had been regarded as a salvage procedure when previous surgery failed, but reported good results in a series of 55 patients who had not had previous surgery. They argue that OCA can be a useful first line treatment especially in patients with large defects. In their case series, the average defect size was 9.6 cm^2.

Bugbee and colleagues[11] provide an overview of OCA in which they note that despite proof of concept evidence going back to the 1980s, there was little use of the technology until the late 1990s, and even then it was carried out mainly in a few specialised centres with local tissue banks.

Evidence

The strength of evidence can be assessed using various checklists, for reviews, randomised trials and observational studies. The ideal evidence for assessing the cost effectiveness would be;

- Evidence of clinical effectiveness based on a large RCT that recruited representative patients followed for long enough to assess all relevant outcomes, including avoidance of knee replacement, compared to best current care
- Assessment of cost-effectiveness based on all costs and benefits

Such evidence does not exist, and if it did, it might no longer be relevant, if the intervention had been superseded by technological advances. This is a common problem with operations and devices, unlike with evaluations of drugs. A drug molecule does not change, whereas devices and procedures evolve. For example, in a recent health technology assessment of autologous chondrocyte implantation (ACI), the longest term outcome data came from forms of ACI that have been superseded by later generations.[12]

Our scoring of some studies may seem harsh, but to some extent, they are being compared with ideal evidence. In practice, we have to make decisions based on best available evidence, imperfect though that may be. Neither policy-makers nor patients are best served if decisions are avoided because "more research is necessary". However, it will often be the case that more research is needed, and systematic reviews often provide a good basis for identifying research needs and

designing future studies. Sometimes the research needs are best met by RCTs, but as will be seen in this review, patient registries can also provide very useful information.

Evidence - reviews

We identified seven recent systematic reviews that covered the use of osteochondral allografts in the knee, some as part of wider reviews, including other interventions. Quality assessment is reported in Table 1. A review by Salzmann et al 2017[13] was concerned with the use of particulated juvenile articular cartilage rather than discrete allografts and was omitted. A review by Seow et al[14] on extracellular matrix and particulate cartilage allografts was also excluded. We did not include the Cochrane review by Gracitelli et al[15] because although the title included allograft transplantation, no studies of OCA were included, because only RCTs were eligible.

Table 1: Quality assessment of reviews of osteochondral allografts in knees

Review	Focused question	Eligibility criteria	Searches	Dual review	Validity	Study details	Publication bias	Hetero-geneity
Assenmacher 2016[16]	Y	Y	Y	NR	Y	Y	N	NA
Campbell et al 2016[17]	Y	Y	Y	Y	Y	Y	N	NA
De Caro et al 2015[18]	Y	Y	Y	Y	N	Y	N	NA
CADTH 2017[19a]	Y	Y	Y	N	Y	Y	Y	NA
Krych 2016[20]	Y	Y	Y	NR	Y	Y	N	Y
Chahal et al 2013[21]	Y	Y	Y	Y	Y	Y	N	NA
Rosa et al 2017[22]	y	y	Y	y	n	Y	n	NA

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported

1. Is the review based on a focused question that is adequately formulated and described?
2. Were eligibility criteria for included and excluded studies predefined and specified?
3. Did the literature search strategy use a comprehensive, systematic approach?
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?
5. Was the quality of each included study rated using a standard method to appraise its internal validity?
6. Were the included studies listed along with important characteristics and results of each study?
7. Was publication bias assessed?
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)

The studies included in the review varied. Some of the differences reflect the aim of the reviews. Assenmacher et al only included studies with a minimum of 9 years follow up. Campbell et al focused on return to sport in athletes and included studies with a minimum follow-up of 12 months, while Krych et al included studies if they reported return to sport outcome measures. De Caro et al looked at fresh allografts for large lesions and only included studies with at least 10 participants and 1 year follow-up. Rosa et al were interested in repairs of failed cartilage repair but also reviewed failure rates in the primary repairs. Chahal et al included studies with a minimum sample size of 10 and a minimum follow-up of 12 months and included studies that were of allograft transplantation alone or in combination with other techniques including meniscal allograft transplantation and osteotomy. The conclusions of the reviews are shown in Table 2

Table 2: Results and conclusions of reviews of OCA in the knee

Results	Conclusions
Assenmacher et al 2016[16]: Long-term outcomes after osteochondral allograft	
5 studies included, mean follow-up across studies 12.3 years, range 10 to 17 years. Gross 2005[23] Levy 2013[24] Salai 1997[25] Torga 2006[26] and Drexler 201 [27] Postoperative Hospital for Special Surgery score mean 84.1. Mean outcome score improvement: Knee Society Function Score, 3 studies, 23.1 (95% CI 10.1-36.0, P < 0.01) Knee Society Knee Score, 2 studies, 26.4 (95% CI, 10.4-42.4, P < 0.01) Lysholm score, 1 study, 53 (95% CI, 27.4-78.6, P < 0.01) Mean failure rate at final follow-up 25% (5 studies) Mean reoperation rate at final follow-up 36% (5 studies) Mean survival (3 studies) at: 5 years 94% 10 years 84% 15 years 71% 20 years 45%	In most (75%) patients, OCA gave good results at a mean of 12.3 years after surgery. The largest drop in graft survival occurred between 15 and 20 years, in a population with mean age 35 at grafting. Most failures went on to total knee replacements. A few had unilateral KR. Failure was variably defined, from graft removal or TKA, to Lysholm and KSS scores <70.
Campbell et al 2016[17]: Return to Sport After Articular Cartilage Repair in Athletes' Knees	
20 studies (ACI 7; OAT 3, osteochondral allograft 1, microfracture 11), median follow-up 3.6 years (range, 1 to 10.4). Rate of return to sports: ACI 84% (p<0.01 vs microfracture) OAT 89% (p<0.001 vs microfracture) Osteochondral allograft 88% (p=0.1 vs microfracture) Microfracture 75% Average time to return to sports: ACI 16.0 months OAT 7.1 months Osteochondral allograft 9.6 months Microfracture 8.6 months Patient-specific factors that influenced outcomes reported (not extracted)	The authors concluded that athletes could return to sports after most interventions, but that microfracture patients were least likely to do so. Only one OCA study was included. (Krych 2012[28])
De Caro et al 2015[18]: Large fresh osteochondral allografts of the knee	

11 studies, mean follow-up 24 months – 13.5 years. Number of failures range 0-31 (percentages not reported). General results presented for individual studies only, limited data. 3 studies reported improvement in symptom and/or function scores. 1 study reported survivorship rate: 89% at 5 yr, 82% at 10 yr, 74% at 15 yr, and 66% at 20 yr	Most studies reported good results, some after long follow-up. All but one study used fresh osteochondral allografts. The authors note that no other effective treatment exists at present for large osteochondral lesions. Cost is identified as the main barrier.
CADTH 2017[19]: The Use of Osteochondral Allograft for the Ankle, Knee, and Shoulder: Clinical Effectiveness and Cost-Effectiveness	
Review of reviews	There were four reviews of OCA in the knee, judged by the CADTH team to e of mixed quality. The quality of the primary studies included in those SRs was also judged to be generally poor, and CADTH advise caution in the interpretation of the findings. The number of primary studies in the knee reviews ranged from one to 19, all case series with no controls. Overall, the review of reviews concluded that OCA reduced pain and improved function in most subjects, and that patient satisfaction was high. A wide range of six to 30 months was reported as the time it took to return to activities or sports. Graft survival was 91-95% at 5 years, 76-85% at 10 years, and 71-76% at 15 years. The largest drop occurred between 15 and 20 years after the operation. Graft failure (defined as further surgery, including knee replacement and graft removal) occurred in 18-25%. One problem was that outcomes for a population not receiving osteochondral allografts were not reported. The authors concluded that prospective RCTs with large samples, longer follow-up, and high quality are needed.
Krych et al 2017[20]: Return to sport after the surgical management of articular cartilage lesions in the knee: a meta‐analysis	
3 allograft studies, follow-up ranged from 24-35 months. Gracitell1 2015[29], McCulloch 2007[9] and Krych 2012[28]. Return to sport was 88%, time to return-to-sports 9.6 (SD 3.0) months	In a wider review of return to sport after cartilage procedures, Krych and colleagues included 3 case series of return to sport after OCA in the knee (including their own 2012 study) with a total of 96 subjects followed up for 24 to 35 months. They concluded that none of the studies provide a high level of evidence. It was notable that the mean defect size was 6.5cm^2 – OCA was being used for larger lesions. In an earlier broader but non-systematic review [30], Krych et al identified six studies of OAC in the knee (only one of

	which was included in the return to sport review) and summarised the benefits of OCA as being; • Both bone and cartilage are replaced • Single operation • The cartilage is hyaline (unlike after microfracture) • Large lesions can be treated. They regarded that disadvantages as being cost, availability and the possible risk of infection. The six studies reported consistently good results. All used fresh allografts. One series reported SF36 but had only 19 patients (Williams et al [31]).
Chahal et al 2013[21]: Outcomes of Osteochondral Allograft Transplantation in the Knee	
19 studies, mean follow-up 58 months (range 19-120) Aggregate mean preoperative IKDC score (6 studies) 37.1, postoperative 64.3 (significant in all studies individually). Aggregate preoperative Lysholm score (4 studies) 39.3, postoperative 70.1 (significant in all studies individually). Aggregate preoperative Tegner score (3 studies) 3.9, postoperative 5.5 (significant in all studies individually). No aggregate survivorship reported (2 studies reported separately) Failure rates 18.1% (review notes differences in definitions and follow-up) Revisions or removals 14%. Serious failures in 2 patients.	Chahal and colleagues included 19 studies, 17 being retrospective and two prospective, with 644 subjects. The Coleman scores were poor (mean 32, range 19 to 45, so no good quality studies). All studies used fresh or fresh-frozen allografts, with none irradiated. Five studies reported on OA in the knee, finding little or none at follow-up in 65% (72 of 110) of patients. Clinical outcomes were consistent and favourable. There was high (86%) satisfaction rate at mean 5 years follow-up.
Rosa et al 2017[22]: How to Manage a Failed Cartilage Repair: A Systematic Literature Review	
12 studies in allografts, mean follow-up not reported Studies were not pooled but discussed separately only.	In patients with no previous cartilage repairs, 13-18% failed after OCA, which was less than after microfracture or mosaicplasty. In patients who had had failures of previous procedures, Rosa et al concluded that OCA was “a safe option.”

ACI, autologous chondrocyte implantation; OAT, osteochondral autograft transplantation

Evidence - Primary studies

Some of the best evidence comes from groups that have built up large cohorts of patients over many years. In addition to overall results, some cohorts have had sufficient numbers to examine subgroups. Table 3 below gives summary details of these and a few other OCA studies. We have not included all the studies covered by the systematic reviews.

Gross and colleagues, Toronto

The earliest reports, with longest follow-up, come from the Mount Sinai Hospital, Toronto group of Allan Gross and colleagues. Their first osteochondral graft in the knee was done in 1972, and they have published several reports over the years. In Gross et al 2005[23], they report results in femoral condyle and tibial plateau separately, for OCAs done 1972-1995, with mean follow-up of 10 years. After 60 femoral OCAs, graft survival was 95% at 5 years, 85% at 10 years, and 74% at 15 years. Mean age at OCA was 27 years (range 15-47). In 12 patients, OCA failed, with nine having TKR. In 65 tibial OCA, mean age at OCA was 42 (range 26-69) years, and 21 failed and had TKR at mean follow-up of almost 10 years. Graft survival was 95% at 5 years, 80% at 10 years, 65% at 15 year, and 46% at 20 years.

In another Toronto paper, Drexler et al 2015[27] report results in a subgroup of 27 consecutive patients who had combined distal femoral osteotomy and tibial OCA following failed tibial plateau fracture, from 1981 to 2005. Median age was 41 (range 17 to 62) years. There were good improvements in clinical scores, and graft survival was 89% at 10 years, 71% at 15 years and 24% at 20 years.

The longest follow-up from the Toronto group was by Raz et al 2014[32], after femoral condyle OCA, with 59% graft survival at 25 years.

Bugbee and colleagues

William Bugbee and colleagues at the Scripps Clinic at La Jolla have built up one of the biggest cohorts of people who have had OCA, with over 800 patients, and have been scientifically very productive. In an overview in 2016 [11], they reviewed their work from basic science, through animal studies and storage methods, to clinical results. They established a clinical database in 1997 with before and after clinical assessment.

In their 2016 article, they provide data on results in 527 knees in 467 patients, mean age 34 (range 14 – 68) having OCA for cartilage injury (35%), OCD (30%), cartilage degeneration (12%), osteonecrosis (8%), early OA (6%).

Results varied by aetiology and history. The best results were seen in patients who had had osteonecrosis (89% graft survival at mean follow-up 5.6 years, range 2 to 20 years, and 85% at 12 years) [11, 33] or after previous cartilage injury (98% at 12 years). Good results were also seen after OCA in patients under 18 year of age with 90% graft survival at 10 years, with good improvement in symptom scales (Murphy 2014[34]). Results were less good in osteoarthritis (41% at 12 years). Results were also less good in bipolar injuries (“kissing lesions”) with 46% failures rate in 48 knees (Meric 2015[35]).

However for many with OA, the alternative (if they were old enough – many would not be, given mean age 34) would be knee replacement. In those patients, OCA of a femoral hemicondyle might provide at least temporary relief of symptoms pending later knee replacement (KR), and function

would be expected to be better than after KR as the cruciates and menisci (if intact) are retained, meaning knee kinematics and possibly proprioception are preserved.

88% of patients had had previous surgery, with an average per patient of two previous procedures. OCA was largely a salvage procedure in a tertiary centre. Briggs et al[10] report that results were better in patients who had not had previous surgery, with OCA survival almost 90% at 5 year and 75% at 10 years, and 61% having some further procedures. Gracitelli et al 2015b[36] reported that OCA after failed previous procedures (including microfracture, mosaicplasty, ACI), in 164 knees, was less successful, with graft survival 82% at 10 years and 75% at 15 years – but still very successful, and accompanied by significant improvements in symptoms. In another study, Gracitelli et al matched 46 patients who had had previous subchondral bone marrow stimulation procedures (microfracture etc) with 46 who had OCA as primary procedure.[37] At 10 years of follow-up, graft survival was similar (86% and 87%) but almost twice as many of the prior marrow stimulation group required subsequent procedures as the primary OCA group (44% versus 24%), with main difference in arthroscopic debridement and meniscal procedures.

Tirico and colleagues[38] examined results of OCA by size of condylar defect in 156 knees from 1998 to 2014. The average graft area was 6.4 cm^2, range 2.3 to 11.5 cm^2. Most (62%) patients had had OCD. Overall graft survival was 97% at 5 years and 93.5% at 10 years, with no difference by graft size, whether measured as absolute area or relative to knee size. Outcomes were broadly similar but benefits were greater in large defects (>8 cm2).

The size of the cohort allows subgroup analysis. Cameron et al 2016[39] report the results of 29 OCA grafts of the femoral trochlea alone (1993-2011) with graft survival 100% at 5 years and 92% at 10 years, and good improvements in clinical symptom scores (see Table 3 for details).

Gracitelli et al 2015a[29] report the results of isolated patellar OCA in 28 knees from 1983 to 2010. Results were not as good as in some other sites, with 78% graft survival at 10 years and 56% at 15 years.

Gortz et al 2010[2] provide results in a series of 28 knees after steroid induced osteonecrosis. The grafts failed in five knees at mean follow-up of 67 months (range 25-235 months), giving a survival rate of about 82%. Most had good symptomatic relief (details Table 3).

Horton et al 2013[40] report results in 33 patients who had a second OCA after the first failed. At 10 years, 61% of the second OCAs, with good symptomatic improvement. The 39% of grafts that failed, did so at mean follow-up of 5.5 years.

Nielsen et al[41] reported a high level of return to sport after OCA, with 79% returning to a high level of performance.

Schmidt et al[42] reported no difference between OCA soon (mean 6 days) after harvest, and after prolonged storage (mean 20 days, range 16-28)

Cole and colleagues, Chicago

Another group with considerable experience is the Rush University Medical Center group in Chicago, Brian Cole and colleagues. An early study by McCulloch et al 2007[9] (graded as fair quality) concluded that OCA was a safe and effective procedure, in a small group of 25 patients in the years 2000 to 2003. They had had several previous procedures (mean of 2.3 operations), and represented a tertiary referral group. There was good improvement in Lysholm scores, from 39 to 67 ($p < 0.0001$)

A series of articles from Frank et al[43-45] reported experience in later years, 2003 – 2014, in 180 consecutive patients with minimum follow-up 2 years. Graft survival was 87% at 5 years. There was no difference in failures rates by age – 13% in over 40s, 16% in under 40s. Nor was there any difference by gender. Concomitant MAT, performed in 36% of patients, caused no problems.

Williams and colleagues, New York

Another long-standing series comes from the New York Hospital for Special Surgery group, with data prospectively collected by Riley Williams and colleagues from 1999. They have provided a series of papers looking at subgroups, showing that results of OCA are no worse in patients who have had ACLR[46] or in those with BMIs over 30 (graft survival 83% at 5 years).[47]. They also found that results in patients aged over 40 (mean age 48, range 40 to 63 years) were also good, with graft survival 73% at 4 years. [48] They have also compared what happens when an OCA graft from the other condyle is used (non-orthotopic grafts) – no difference in results.[49]

The New York group have treated elite and other high performance athletes, and Krych et al 2012[28] and Balaz et al 2018[50] have reported high proportions returning to high level performance.

The group has also assessed results with decellularised osteochondral plugs which can be obtained "off the shelf" but Johnson et al[51] reported that results in 36 patients, in 2014-15, were poorer than with fresh allografts, and were not recommended.

Other studies

Two small fair quality studies by Brown et al[52] and LaPrade et al[53] with 34 and 23 patients, currently have only short duration of follow-up (2 and 3 years respectively). Brown reported that 26.5% of participants had subsequent procedures related to the OCA with one converted to TKR by 2 years of follow-up. LaPrade reported that 17% had had additional procedures by 3 years of follow-up. Both Brown and LaPrade reported improvements in IKDC scores. Brown reported significant improvements in KOOS quality of life scores at 2 years.

Pearsall et al 2011[54] compared fresh (18) and frozen (9) OCA plugs and found more failures (TKR) with frozen (6 of 9). There were statistically significant improvements in both Knee Society Score (KSS) and WOMAC.

Table 3: Osteochondral allograft studies

Reference	Aim	Population	Study details	Key results
Studies from the Scripps Clinic, La Jolla group, Bugbee et al. This group set up a database to prospectively collect data and they now have data going back for over 20 years.				
Bugbee et al [11]	To provide an overview of OCA in cartilage repair, with a review of results from the La Jolla centre	527 knees in 467 patients, mean age 34 (range 14 – 68) having OCA for cartilage injury (35%), OCD (30%), cartilage degeneration (12%), osteonecrosis (8%), early OA (6%). 88% of patients had had previous surgery. Femoral condyle lesions large (mean 8cm^2, range 1 to 27 cm^2). OCA largely a salvage procedure in a tertiary centre.	Data from prospective clinical database starting 1997. Before and after assessment with D'Aubigne and Postel scale.	The majority of patients improved: 93% less pain, 96% satisfied, 90% would do it again. Success varied by conditions, with best results (86% and over) amongst those with no previous surgery, adolescents, and after osteonecrosis, and poorest (63% good to excellent) in revision OCA. OCA for OA knee not as effective as in the aforementioned conditions, but can provide an alternative to knee replacement.
Briggs 2015 [10] Conference abstract.	To assess OCA transplantation for cartilage injury in patients with no previous surgical treatment.	OCA transplantation as primary treatment for a chondral or osteochondral defect, any age, no prior surgical treatment of an isolated, Grade III or IV chondral or osteochondral defect, minimum 2-year follow-up. From 1983 onwards. Commonest problems OCD (44%) and avascular necrosis (31%)	Sample size: 55 (61 knees) Follow-up: mean 7.6 years (range 1.9-22.6) Data source: prospective database	Pain and function improved (P < 0.01). OCA survival was 89.5% at 5 years and 74.7% at 10 years. 29.5% had further surgery (11 OCA failures and 7 other surgical procedures). Of the 11 OCA failures, (mean time to failure 3.5 years; range 0.5-13.7), 8 had TKR, 2 had OCA revisions, and 1 had a patellectomy.
Cameron 2016[39] Cameron 2015[55]	To evaluate graft survivorship and clinical outcomes in patients who	OCA transplantation of the femoral trochlea alone 1993-2011, age >12 years.	Sample size: 28 (29 knees)	Graft survivorship was 100% at 5 years and 91.7% at 10 years. One patient converted to TKA after 7.6 years.

	had OCA to the femoral trochlea.		Follow-up: 7.0 years (range 2.1-19.9)	Mean modified d'Aubigne´-Postel score improved from 13.0 to 16.1, KS-F score from 65.6 to 85.2, and IKDC total score from 38.5 to 71.9; the mean UCLA score was 7.9 postoperatively and KOOS QOL scores improved from 34.0 to 75.1.
Emmerson 2017[56]	Hypothesis: Fresh osteochondral allograft transplantation will provide a successful surgical treatment for osteochondritis dissecans of the femoral condyle.	Patients who had undergone treatment for osteochondritis dissecans of the femoral condyle and had a minimum of 2 years of follow-up, 1980-2003. (Paper also says since 1983, not 1980). May be some overlap with the patients in the Sadr 1997-2013 group.	Sample size: 64 (66 knees) Follow-up: mean 7.7 (range 2-22) years.	15% underwent reoperation. The mean clinical score improved from 13.0 preoperatively to 16.4 postoperatively (P < 0.01).
Gracitelli 2015a[29]	To evaluate functional outcomes and survivorship of the grafts among patients who underwent OCA for patellar cartilage injuries.	Patients who had undergone an isolated OCA of the patella between 1983 and 2010. Indications: isolated patellar lesions with ICRS grades 3 and 4, patients who had failed previous surgical and nonsurgical interventions, and/or who wished to avoid prosthetic arthroplasty	Sample size: 27 (28 knees) Follow-up: mean 9.7 (7.5) years	60.7% had further surgery 28.6% were considered OA failures (4 conversions to TKA, 2 conversions to patellofemoral knee arthroplasty, 1 revision OCA, 1 patellectomy). Patellar allograft survivorship was 78.1% at 5 and 10 years and 55.8% at 15 years. Pain and function improved from the preoperative visit to latest follow-up.
Gracitelli 2015b[36]	To assess the outcome of OCA transplantation as a salvage procedure after various cartilage repair surgeries	Underwent cartilage repair surgery prior to OCA transplantation and minimum follow-up of 2 years. Patients with failed previous SMS, OAT, implantation of synthetic bone	Sample size: 163 (164 knees) Follow-up: 8.5 years (SD 5.6)	41.5% of knees had reoperations after OCA transplantation. 18.9% of knees were classified as allograft failures. Median time to failure was 2.6 years (SD 6.8, range 0.7-23.4). Survivorship of the graft was 82% at 10 years and 74.9% at 15 years.

		plugs, or ACI were included. 1983-2011.		Scores on all functional outcomes scales improved significantly from preoperatively to latest follow-up.
Gracitelli 2015c[37]	To compare the outcomes of a retrospective matched-pair cohort of (1) primary OCA transplantation and (2) OCA transplantation after failure of previous SMS.	Consecutive series with OCA as a primary treatment, (group 1), matched to a non-consecseries that underwent OCA transplantation after failure of previous SMS (group 2). Minimum follow-up of 2 years. 1983-2011.	Sample size: 92 (group 1 46, group 2 46) knees Follow-up: group 1 7.8 (SD 5.1 years), group 2: 11.3 (SD 6.6 years)	24% in group 1 had reoperations, compared with 44% in group 2 (P = 0.04). The OCA was classified as a failure in 11% of knees and 15% of knees) in group 2 (P = 0.53). At 10 years of follow-up, survivorship of the graft was 87.4% and 86% in groups 1 and 2, respectively. Both groups showed improvement in pain and function on all subjective scores from preoperatively to the latest follow-up (all P <0.001).
Görtz 2010[2]	To ask if fresh OCAs would (1) heal to host bone in the presence of osteonecrosis, (2) provide a clinically meaningful decrease in pain and improvement in function, and (3) prevent or postpone the need for arthroplasty.	Corticosteroid-associated osteonecrosis, age <50 years (1984-2006)	Sample size: 22 (28 knees) Follow-up: mean 67 months, range 25–235	5 knees failed. Graft survival rate 89% Mean D'Aubigne´ and Postel score improved from 11.3 to 15.8; 76% had a score > 15. Mean IKDC pain score improved from 7.1 to 2.0, mean IKDC function score from 3.5 to 8.3, and mean Knee Society function score from 60.0 to 85.7.
Horton 2013[40]	To evaluate outcomes of patients who have undergone revision osteochondral allograft transplantation of the knee.	Revision OCA in the knee, ≥ 2 years from surgery, and minimum 2 years' follow-up. 1983-2012.	Sample size: 33 Follow-up: mean 10 years (range 2.4-26) for those with grafts surviving	39% had failed results after revision OCA transplantation, mean time to failure 5.5 years. The remaining 61% had surviving revision allografts, mean graft survival 10 years. Mean pain and function scores at the last follow-up were improved.

Levy 2013[24 24]	To determine (1) pain and function, (2) frequency and types of reoperations, (3) survivorship, and (4) predictors of OCA failure	OCA of the femoral condyle (1983-2001). Indications: presence of a painful chondral or osteochondral lesion(s) of the femoral condyle and failure of previous nonsurgical or surgical treatments.	Sample size: 122 (129 knees) Follow-up: median 13.5 years, (range 2.4-27.5)	Mean modified Merle d'Aubigne´-Postel score improved from 12.1 to 16, mean IKDC pain score from 7.0 to 3.8, mean IKDC function score from 3.4 to 7.2, and mean KS-F score from 65.6 to 82.5. 47% of knees underwent reoperations. 24% of knees failed at a mean of 7.2 years. 10 year survivorship 82% 15 year survivorship 74% 20 year survivorship 66%
Meric 2015[35]	To evaluate the outcomes of patients who had undergone OCA transplantation for reciprocal bipolar cartilage injuries (''kissing lesions'') of the knee	OCA transplantation for bipolar cartilage lesions of the knee from 1983 to 2010. Indications: reciprocal lesions in the patellofemoral joint and tibiofemoral joint, ICRS grades 3 and 4, failed previous surgical and nonsurgical interventions and/or wished to avoid prosthetic arthroplasty.	Sample size: 46 (48 knees) Follow-up: 7 years (range 2.0-19.7).	Survivorship of the bipolar OCA was 64.1% at 5 years. 63% of knees underwent further surgery; 46% were considered failures (3 OCA revisions, 14 total knee arthroplasties, 2 unicondylar arthroplasties, 2 arthrodeses, and 1 patellectomy). Mean modified Merle d'Aubigne´-Postel score improved from 12.1 to 16.1; 88% of surviving allografts scored ≥15. Mean IKDC pain score improved from 7.5 to 4.7, mean IKDC function score improved from 3.4 to 7.0. Mean KS-F score improved from 70.5 to 84.1.
Murphy 2014[34] Earlier report Pennock 2013 (abstract only)[57]	To describe a 28-year experience with OCA transplantation in patients younger than 18 years with	Paediatric and adolescent patients with fresh OCA transplantation in knee; <18 years at time of surgery and ≥ 2	Sample size: 39 (43 knees)	11.6% knees experienced clinical failure at median of 2.7 years (range, 1.0-14.7). Four failures were salvaged successfully with another OCA

	a focus on subjective outcome measures, return to activities, and allograft survivorship.	years past date of index surgery. 1983 onwards. Aetiologies: osteochondritis dissecans, avascular necrosis, traumatic chondral injury, degenerative chondral lesion and fracture.	Follow-up: mean 8.4 years (range 1.7-27.1)	transplant. One patient underwent prosthetic arthroplasty 8.6 years after revision allograft. Graft survivorship was 90% at 10 years. Of the knees with grafts in situ, 88% rated good/excellent (18-point scale). Mean IKDC improved from 42 preoperatively to 75 postoperatively, and Knee Society function score improved from 69 to 89 (both P<0.05).
Nielsen 2017[41]	To determine if athletic patients undergoing OCA transplantation returned to sport, assess reasons for not returning to sport, and ascertain patient and graft-related characteristics that differed between those who returned or did not return to sport. The secondary aims were to assess graft survivorship and patient-reported subjective outcome measures (pain, function, satisfaction) among athletic patients undergoing OA transplantation.	Primary OCA transplantation by single surgeon 1998-2014, participated in sport or recreational activity before the cartilage injury, and did not undergo major concomitant surgery (osteotomy, anterior cruciate ligament [ACL] reconstruction, or meniscal allograft) at the time of OCA transplantation.	Sample size: 142 (149 knees) Follow-up: 6 years (range 1.0-15.8)	75.2% of knees returned to sport or recreational activity. 79% were able to participate in a high level of activity (moderate, strenuous, or very strenuous) postoperatively. After OCA transplantation, 25.5% of knees underwent further surgery; 14 knees (9.4% of entire cohort) were considered allograft failures. Among the 135 knees that had the graft remaining in situ, pain and function improved from preoperatively to the latest follow-up on all measures.
Sadr 2016[33] Earlier abstract Sadr 2014 [58]	to determine the clinical outcome of a large cohort of patients (juvenile and adult) who received fresh OCA	Patients who had undergone OCA transplantation for OCD (type III or IV) by a single	Sample size: 135 (149 knees)	23% had reoperations, of which 8% were classified as failures (7 OCA revisions, 3 unicompartmental knee arthroplasties, and 2 total knee

	transplantation for the surgical management of osteochondritis dissecans (OCD) after failure of other treatments.	surgeon, 1997-2013, minimum 2 years follow-up. The 2014 abstract reported results from an earlier but overlapping period, 1983-2010, with 181 knees in 164 patients.	Follow-up: 6.3 years (range 1.9-16.8)	arthroplasties). OCA survivorship was 95% at 5 years and 93% at 10 years. Of the 137 knees whose grafts were still in situ at the latest follow-up, the mean modified Merle d'Aubigne´ and Postel score was 16.8; IKDC pain, function, and total scores were 2.1, 8.1, and 82.3; and KS-F and KS-K scores were 95.7 and 94.3, respectively. In the earlier period 31% had re-operations with 13% classed as failures.
Schmidt 2017[42]	To investigate the relationship between prolonged fresh graft storage and clinical outcomes of OCA transplantation.	Patients who received ''early release'' grafts 1997-2002 (mean storage time 6.3 days, range 1-14) or ''late release'' grafts 2002-2008 (mean storage time 20.0 days range 16-28). Minimum follow-up of 2 years	Sample size: 150 (75 early release, 75 late release) Follow-up: early release: 11.9 years (range 2.0-16.8), late release: 7.8 years (range 2.3-11.1)	Failure occurred in 25.3% of the early release group and 12.0% of the late release group (P = 0.036). Median time to failure 3.5 years (range 1.7-13.8) and 2.7 years (range 0.3-11.1) for the early and late release groups, respectively. The 5-year survivorship of OCAs was 85% for the early release group and 90% for the late release group (P = 0.321). No differences in postoperative pain and function between the groups.
Tirico 2018 [38]	The aim of this study was to assess success of OCA by size of defect.	Patients who had OCA from 1998 to 2014 for isolated lesions of a femoral condyle. 62% had OCD.	156 knees in 143 patients. Mean age 29.6, 63% male. Mean graft area 6.4 cm^2, range 2.3 to 11.5 cm^2. Mean follow-up 6 years.	Overall graft survival was 97% at 5 years and 93.5% at 10 years, with no difference by graft size, whether measured as absolute area or relative to knee size. Outcomes were broadly similar but benefits were greater in large defects (>8 cm2).
Studies from the Chicago group, Brian Cole and colleagues. This is another group that has built up a prospective database.				

McCulloch 2007 [9]	To assess results of prolonged fresh OCA grafting, stored for up to 42 days.	25 consecutive patients having fresh prolonged storage OCA grafts for resurfacing of full-thickness cartilage defects of at least 2 cm^2 in the femoral condyle. Mean age 35, range 17-49. 72% male. Mainly (68%) medial condyle. 96% had had previous procedures, including 18 meniscectomies and 11 microfractures. Mean number of prior procedures (excluding diagnostic arthroscopy) was 2.3 and they were mostly a tertiary referral group. Concomitant procedures 60%: meniscal transplantations, opening wedge high tibial osteotomies, and removal of previous osteotomy plate.	Minimum follow-up 2 years, mean 35 months, range 24 to 67 months. Concomitant procedures 10 MAT and 4 HTOs. Mean age 35 (range 17 to 49). Years 2000 to 2003	Improvements in Lysholm (39 to 67), IKDC (29 to 58), and all KOOS components, including significant improvements in KOOS QoL at 2.9 years follow-up. Statistically significant improvements in SF-12 physical component but not SF-12 mental component. 88% of grafts incorporated into host bone. Little difference in results between OCA alone and OCA + MAT groups. At 2.9 years follow-up, 8% had failure secondary to allograft fragmentation (allograft removal followed by a microfracture) or marked pain for more than 6 months. Conclusion: prolonged storage is safe in OCA grafting.
Frank 2017[43] Frank 2018[44] Frank 2018[45]	To assess survival for OCA transplantation and report findings at reoperations To compare results for male and female patients under and over 40 years of age.	Consecutive patients undergoing primary OCA transplant by a single surgeon 2003-2014, with minimum follow-up 2 years. Included if they had undergone prior ipsilateral knee surgery (other than prior OCA) or concomitant procedures (including MAT, ligament reconstruction, and/or corrective realignment procedures).	Sample size: 180 Follow-up: 5.0 (SD 2.7 years)	37% had reoperation at a mean of 2.5 (SD 2.5 years). 87% allograft survival at mean 5 years after OCA. Failures in 13% at a mean of 3.6 (SD 2.6) years, defined as revision OCA transplant (n = 7), conversion to arthroplasty (n = 12), or arthroscopic appearance of a poorly incorporated allograft (n = 5). Excluding the failed patients, statistically and clinically significant improvements were found in the

		36% had MAT at same time as OCA.		Lysholm score, IKDC score, KOOS, and SF–12 PCS at final follow-up (P < .001 for all). Patients who needed reoperation also improved but less so. No differences by age in reoperation rate, time to reoperation, or failure rate (>40 years: 13%; ≥40 years: 16%). No significant differences in number of complications, outcome scores, or time to failure between the sexes. Concomitant MAT caused no problems.
Studies from the Mount Sinai Hospital, Toronto group, Allan Gross and colleagues				
Gross 2005[23] Abstract: Aubin et al 2001 [59]	To examine the long term clinical and radiological results as well as the survivorship of fresh OCAs for post-traumatic defects around the knee. The long-term clinical outcomes and survival analysis are presented for patients a minimum of 5 years from OA transplant surgery of the medial or lateral femoral condyle for post-traumatic unipolar defects.	Traumatic unipolar osteochondral defects of at least 3 cm in diameter and 1 cm deep, age <60 years (1972-1995)	Sample size: femoral condylar grafts 60; tibial plateau grafts 65 Follow-up: femoral condylar 120 months, range 58–259; tibial plateau 11.8 years, range 2–24 Data collection: prospectively collected database	Femoral condylar grafts: Graft failures: 12 (3 removal, 9 total knee replacement) 5 year survivorship 95% 10 year survivorship 85% 15 year survivorship 74% Of those with surviving grafts, HSS was 83 points. Transplant to medial or lateral condyle had no bearing on long term outcomes. Of 38 with radiographs, 48% had no or mild arthritis, 26% had moderate and 26% had severe arthritis. Tibial plateau grafts: Conversion to TKA: 21 5 year survival 95% 10 year 80% 15 year 65%

				20 year 46%
Drexler 2015[27]	To examine the long-term survivorship and functional outcome of distal femoral varus osteotomy with focal OCA following failed lateral tibial plateau fracture surgery	Consecutive series (1981-2005) of distal femoral varus osteotomies combined with focal OCA. All had previous open reduction with internal fixation surgery of a lateral tibial plateau fracture, with continued lateral knee pain. Median age at OCA 41 years, range 17-62.	Sample size: 27 Follow-up: median 13.3 years, range 2–31 Data collection: medical records and database	KSKS increased from median 54.6 to 83.8 points at 2 years (p<0.01), still at end of follow-up. KSKS increased from medial 50.6 to 71.1 at 2 years (p<0.01), still significant at end of follow-up. 10 year survivorship 88.9% (± 4.6) 15 year survivorship 71.4% (± 18.1) 20 year survivorship 23.8% (± 11.1)
Raz 2014[32]	To examine the long-term survival and clinical outcomes of fresh OCA for posttraumatic and osteochondritis dissecans defects in the knee.	Unipolar OCA transplant to the femoral condyle >15 years from time of search, 1972-1995. Age <50 years at surgery, presented with a posttraumatic osteochondral or osteochondritis dissecans defect limited to the distal aspect of the femur (unipolar) and was larger than 3 cm in diameter and 1 cm in depth.	Sample size: 58 Follow-up: mean 21.8 years (range 15- 32) Data collection: database	13/58 (22.4%) required further surgery; 3 underwent graft removal, 9 converted to TKA, 1 underwent multiple debridements followed by above-the-knee amputation. Three died due to unrelated causes. Kaplan-Meier analysis of graft survival showed rates of 91%, 84%, 69%, and 59% at 10, 15, 20, and 25 years, respectively. Patients with surviving grafts had good function, with a mean modified HSS score of 86 at 15 years or more.
Articles from the New York Hospital for Special Surgery group. These papers were based on data from a prospective registry started in 1999 by R J Williams.				
Krych 2012[28] Possible partial overlap with Balazs 2018[50].	To review the rate of return to athletic activity after OCA transplantation in the knee and to identify any potential risk factors for not returning to sport. No details of which sports. Balazs 2018 basketball only.	Patients who regularly participated in sports before articular cartilage injury with isolated chondral and osteochondral lesions of the knee, ≥2.5 cm^2 and without generalized osteoarthritis, age	Sample size: 43 Follow-up: mean 2.5 years (rage 1-11) Data collection: registry	Limited return to sport possible: 88% Return to pre-injury level: 79% (time to return 9.6 (SD 3.0) months). Balaz reported 80% return to sport with no reduction in performance level, after mean 14 months (range 6 to 26 months).

		18-50 years (2000-2010). Fresh OCA. Balaz reported results in 11 basketball players who had full-thickness cartilage injuries, four professional and 7 college players. 14 treated lesions, mainly lateral condyle and trochlea. Mean defect size 5.1 cm^2.		
Wang 2017[49]	To compare the clinical outcomes of patients treated with non-orthotopic (lateral-to-medial condyle or medial-to-lateral condyle) OCA with those treated with traditional orthotopic (medial-to-medial condyle or lateral-to-lateral condyle) OCA.	Inclusion criteria: skeletal maturity; symptomatic focal cartilage lesions of the medial or lateral femoral condyle classified as Outerbridge grade III or IV at the time of arthroscopic surgery and not involving substantial bone loss requiring additional bone-grafting; treatment with fresh OCA; minimum 2 years follow-up.	Sample size: 77 (orthotopic 50, non-orthotopic 27) Follow-up: orthotopic 4.4 years (range 2-16), non-orthotopic 3.4 years (range 2-11) Data source: registry	Reoperation ($p = 0.427$) and failure ($p = 0.917$) rates did not differ significantly between groups. Both groups demonstrated significant increases in the SF-36 physical functioning and pain, IKDC, and Knee Outcome Survey-Activities of Daily Living (KOS-ADL) scores compared with baseline ($p < 0.004$). Outcome scores (baseline and postoperative) and change scores did not differ significantly between groups.
Wang 2017 [46]	Aim: to compare outcomes of OCA in patients who had had ACL reconstruction with those with intact ACLs. Hypothesis: ACLR does not normalise knee kinematics so OCA may be more likely to fail.		50 ACL intact and 25 ACLR. Minimum follow-up 2 years, mean 3.9 years, range 2-14). Mean age 36	% year OCA graft survival 79% with intact ACL and 85% with reconstructed. So OCA is not less successful in patients with ACLR.

Wang 2018 [48]	OCA in patients aged over 40.		51 patients aged 40-63, mean 48 years. 14 (27%) had had previous repair attempts (mainly MF) and 12 had had previous ACLR.	14 (27%) OCA failure at 4 years, one revision OCA, 5 UKR, 8 TKR. Higher failure rates with more prior surgery and baseline OA KL of 2 or more. Failure rate higher than in younger populations from other studies, but still 73% graft survival at 4 years. 88% at 2 years
Wang 2018[47]	OCA in patients with BMI >30. 2000 to 2015	74% had had previous surgery. Mean BMI 33, range 30-39.	31 patients mean age 35. Mean BMI 33, range 30-39.	5 year OCA graft survival 83%. Substantial symptomatic improvement. So BMI > 30 should not rule out OCA.
Other studies				
Brown et al, 2011[52] Portland, Oregon USA	OCA transplant to repair grade 4 International Cartilage Repair Society articular cartilage defects of the femoral condyle, 2006-2008	Aetiology: OCD (11), focal OA (23), avascular necrosis (2). Nine (26%) had concomitant procedures including ACL reconstruction, tibial osteotomy, medial patellofemoral ligament reconstruction/ lateral release, meniscus transplant.	Follow-up: 2 years Sample size: 34 (45 grafts). Average lesion size 5.7 cm^2, range 1.5-15 cm^2.	Significant improvement in pain and sports/recreation function, but not in symptoms or activities of daily living. Significant improvements in KOOS QoL at 2 years. IKDC improved from 45 to 62. One patient required TKR after 2 years.
LaPrade et al 2009[53] Minnesota	Main indication was presence of a symptomatic full-thickness articular cartilage defect of >3 cm^2 on the femoral condyles. Consecutive cases from 2002. All grafts were refrigerated.	23 patients. Mean age 31 (16 to 47) years. 57% male. 83% medial condyle. 17.4% had additional procedures including tibial osteotomy if required, and patients with >50% loss of the meniscus in the affected compartment had concurrent MAT.	Follow-up mean 3 years, range 1.9 to 4 yrs.	Statistically significant improvements on CKRS overall and individual component scores. IKDC improved from 52 to 68 ($p < 0.03$)
Pearsall et al, 2011[54]	Aim: to compare success of OCA with refrigerated and	Tegner 3 or greater activity level; articular cartilage damage	Age : 48 (17-69) % male: 68.8	Six failures (all refrigerated) had KR. 76% survival at 4 years. Mean

University of South Alabama, USA Earlier study, Pearsall et al 2008 [60] may have some patients in common	frozen allografts. "Fresh" allografts defined as harvest within 24 hours of donor's death and time from harvest to implant 7 days or less.	limited to 1 or 2 compartments; biomechanical knee alignment that was less than 5° of varus or valgus or correctable with a distal femoral or proximal tibial osteotomy; and failure of conservative measures including non-steroidal anti-inflammatory medications and physical therapy for a minimum of 3 months. Not explicitly reported but a proportion had tibial or distal femoral osteotomies.	Follow-up: average 46 months (range 24-60) Sample size: 26 1998-2002 18 refrigerated and 9 frozen grafts. (2008 paper had 12 and 12)	WOMAC score improved from 46 to 66, and KSS from 104 to 132. Statistically significant improvements in the Knee Society Score (KSS) The paper mentions allograft "plugs" so may have used a mosaicplasty technique rather than single large OCAs.
Shaha 2013[61] Hawaii	To assess the ability of an active-duty military population to return to a preinjury level of duty/activity after treatment of a large chondral defect with OCA transplantation	Active-duty military population who underwent OCA (2002-2011). Indication: symptoms were sufficient to limit their activity and ability to function in their occupational role and they had failed to improve with non-operative management	Sample size: 38 Follow-up: mean 4.1 years (range 0.6-8.9) Data collection: database	Overall rate of return to full duty: 28.9% Return to limited activity: 28.9% Unable to return to military activity: 42.1% Return to pre-injury level of sport: 5.3% These results are much poorer than in most case series.

ACI: autologous chondrocyte implantation; ICRS: International Cartilage Repair Society; KS-F, Knee Society Function score; OCA: Osteochondral Allograft; OA osteoarthritis; OAT: osteochondral autograft transplantation; SMS: subchondral marrow stimulation; TKA: Total knee arthroplasty; UCLA: University of California, Los Angeles activity score; UKA: Unicompartmental knee arthroplasty

Discussion - OCA

The aims of repair are to eliminate symptoms, restore the normal biomechanics in the knee, and prevent the development of osteoarthritis and the need for knee replacement. (Massachusetts Blues policy statement Nov 2017).[62]

The results of OCA are generally good. In most cases, there are no other satisfactory options, because most subjects are too young for knee replacement.

Without OCAs, many of these patients are destined to develop early and severe OA. As noted by Heir et al [63] some already have considerable impairment in quality of life. Treatment would be by analgesics and rehabilitation such as physiotherapy.

The Assenmacher review[16] summarised mean long-term survival from three studies as;

5 years = 94%

10 years = 84%

15 years = 71%

20 years = 45%

Sherman and colleagues[64] reviewed five studies and reported survivals of 85% to 100% at 5 years, 71% to 97% at 10 years, 74% to 76% at 15 years and up to 66% at 20 years. However they noted poorer results in people with pre-existing OA, and in patello-femoral lesions.

Even when OCAs fail, most of the failures occur after a considerable time, such as after 15 years. They can therefore postpone knee replacement until an age range where the total knee replacement (TKR) may be more acceptable to the patient and may not need to be revised. Some patients may have unicompartmental knee replacement (UKR) first, a lesser procedure than TKR, but which may later be revised to TKR.

Both Sherman et al[64] and Rosa et al[22] regard OCA as the best option after failure of ACI, microfracture and mosaicplasty.

While OCA is regarded as the treatment of choice as a salvage procedure, it is not clear why it was originally regarded by some as only a salvage procedure, given its high success rate. Gracitelli et al [37] reported the results of OCA in two groups of patients, in 46 knees where OCA was the primary treatment, and in 46 knees where OCA followed previous marrow stimulation surgery such as microfracture. Mean age was 27. Both groups did well with failures in 11% in those with no previous repair attempts, and 15% in the previous repairs group. About half the failures had OCA revision, and half had TKR. By 10 years, survival was no different. Gracitelli et al attribute this to the technique used in OCA, wherein 3-8mm of subchondral bone is removed and replaced, including the layer damaged by previous procedures.

We note a 2016 policy document from United Healthcare[65] which, based on a review of some studies, concludes that OCA in the knee is recommended, subject to some restrictions, but that OCA in other joints is considered to be unproven. A similar statement was issued by the Blue Cross Blue Shield in Massachusetts (Policy number 111, issued November 2017)[62] saying that OCA was approved for large full thickness chondral defects of the knee, where large could be 10 cm^2. OCA was considered to be “investigational” (which we take to mean for research studies only) in other joints. Particulate cartilage repair was also considered to be investigational.

Limitations

In this chapter, we have not examined preservation methods, apart from assuming that irradiated allografts are now little used. There is a considerable literature on preservation systems, comparing fresh and frozen, and if fresh, storage temperatures, and their effect on chondrocyte viability. Most systems store allografts at 4 degrees C. The Missouri Osteochondral Preservations System (MOPS) stores them at room temperature (~ 25 degrees C) and is reported to preserve chondrocyte viability for longer (56 days) than in refrigerated allografts.[66, 67] Capeci and colleagues[1] provide a good review.

LaPrade et al[53] checked the viability of allografts refrigerated for more than 14 days before implantation (to allow time for checking for infection in donors) but less than 28 days (because chondrocyte viability had been reported to decline thereafter). They followed up 23 graft recipients for an average of 3 years. The allografts had been stored for an average of 20 days, range 15 to 28 days. There were no graft failures.

The most serious limitation in the evidence reviewed above is the absence of control groups. The studies are mostly before and after studies, which do not give data on the effectiveness of OCA over no, or only non-surgical treatment. We therefore have to rely on observational studies of untreated osteochondral or chondral defects.

Messner and Maletius[68] reported progression of OA in 28 athletes with symptomatic chondral defects over a 14 year period, with joint space narrowing, and Link and colleagues[69] showed that MRI changes correlated with clinical symptoms.

Economic analysis

Our knee model starts from the decision to insert OCA. We assume that any patients with sufficient malalignment to require osteotomy, would have that done first (or at the same time). So the arms of the study are intervention with OCA, and conservative care.

We considered having an arm with metal patches, but decided that these were still experimental with insufficient data. A high revision rate was reported with the HemiCAP-Wave patch[70] with 5 of 18 patients who had the 2009-2012 version requiring revision to TKR by 6 years. (Mean age at entry was 51.) However this high revision rate may have been an outlier, because Becher and Cantillier[71] reviewed five other studies, wherein the revision rate was only about 10%. Their review was not fully systematic but they checked all reference lists of retrieved studies and applied the Coleman quality score. They reported the results of 169 HemiCAP implants, most successful. However follow-up KOOS scores were given but not baseline ones, so the amount of benefit cannot be determined.

Data on a more recent device, the second version of the Episealer, is as yet sparse, with two published accounts with 10[72] and two[71] patients. However such patches may be an option in future once more data are available. One problem with assessing such devices is that they continue to evolve and long-term results may come from superseded versions.

Failures after OCA arm can be considered for a second OCA, or can go down the same pathway as the no-surgery group. However most will do well, with over half still successful at 15 years. Some will then fail, but patients may then have reached the age at which knee replacement is acceptable. So

the effect of OCA, over a 30-year period, is to avoid KR in many, and to delay it in others. The delay reduces the likelihood of revision TKR being required.

Modelling

Conservative care will include symptomatic relief with analgesics, and may also include supportive care with physiotherapy. The underlying osteochondral defect will not be affected by these, and patients will progress to osteoarthritis and in due course, knee replacement, which may be unicompartmental. If symptoms become severe, they may be considered for earlier than usual knee replacement, with the acceptance that the initial arthroplasty will not last a lifetime, and that one or two subsequent revisions will be required.

A major driver in the modelling is knee replacement costs, which depend on the number of replacements per patient per lifetime. Bayliss and colleagues[8] used the UK Clinical Practice Research Datalink to examine replacement revision rates by age of first replacement. People aged 70 or over at first TKR had only about a 5% chance of needing a revision in their life time, but people younger at TKR had a much higher chance, with the highest reported being a 35% revision rate in men age 50-54 at TKR. The rate amongst women was about 20% lower. In addition, the mean duration in these men from TKR to revision was only about 5 years, meaning that a second revision/ 3rd TKR was likely.

The higher revision rate in men may be linked with return to sport. In a systematic review, Witjes and colleagues[73] found that most of 3261 men had returned to sporting activities three months after a TKR. Dagneaux and colleagues[5] conclude that most people can return to intermediate activities but that return to sport should be gentle and progressive.

So if OCA can avoid revision in most people, or postpone it in others, it can mean that first TKR is at least delayed, and that the need for revision TKR is reduced. For example if OCA in a 40 year-old can give a good result for 20 years, first TKR at age 60 is much less likely (about 15%) to need to be replaced than a first TKR at age 50 (35%).

The evidence on TKR under age 50 is sparse, and as noted by Lonner et al[74], most TKR in the under 50s is done for rheumatoid arthritis, not OA, and so not relevant to this review. (RA is a systemic disease and if someone has severe RA with TKR at, say, age 40, they are likely to have other joints affected and to be physically less active, and unlikely to be taking part in activities that confer a high risk of revision being required.) Lonner and colleagues reported the results of TKR in 32 patients with OA, who had the procedure under 40 years of age. Good results were seen in 91% (no revision needed) or 87% (either revision or radiological evidence of loosening) at mean follow-up 8 years (range 5 to 17 years). The TKRs were done from 1982-1994. However the 9% revision rate at 8 years may not be sustained at longer durations.

A proportion, perhaps 30%, will have UKR, because they have single compartment OA. However the use of UKR appears to vary regionally and internationally.

A considerable proportion of people with osteochondral defects have or had OCD. The natural history of this has been reported in several studies. Linden[3] followed up 67 knees in 58 patients for a mean of 33 years. These patients had had onsets in childhood (mean age 13) or as adults (mean age 29) 80% were on the medial condyle. Internal fixation was not used, and most had arthrotomy and removal of fragments. The results were strikingly different for adult and childhood onsets. At mean follow-up 33 years, none of the childhood onset cases had severe OA, and few had mild. Of the adult onset cases, over 60% (33/53) had severe OA. The pain of OA came on about 20 years after injury.

Anderson and Pagnani[75] reported that of 19 patients who had OCD fragments removed, eight had severely abnormal IKDC after as little as 5 years (range 5 to 20 years). Unlike in the Linden study, no significant differences were seen between those whose OCD developed before growth ended. Twyman and colleagues[4] also reported poor outcomes in a series of 22 patients with onset of OCE before skeletal maturity. After 34 year follow-up, a third had moderate or severe OA.

Cotter and colleagues[76] report a series of patients who had had an unsuccessful previous repair attempt after OCD (mostly microfracture, open fixation and loose body removal), and then had OCA. At a mean follow-up of 7.3 years, 82% had returned to sport and were satisfied with the results of surgery. This study was not included in a systematic review by Lamplot et al[77] of treatment of failed cartilage repairs. Lamplot et al found three studies of the use of OCA after failed repairs, mainly microfracture, and noted that, unlike with ACI, previous MF did not reduce the success rate of OCA.

Return to sport after OCA was also reported by Nielsen et al[41] in a series of 142 patients, about half of whom were highly competitive athletes, with the rest described as "well-trained and frequently sporting". 75% returned to sport, including at strenuous levels.

The poorest return to previous activities was reported by Shaha et al[61] in Hawaii, in US soldiers. They found that 42% (16/38) were unable to return to full military duties after OCA, especially if their military activity included combat.

A natural history study of articular cartilage defects was carried out by Shelbourne et al[78]. The defects had been incidental findings in people having ACL repair. Patients with cartilage defects were matched with others have ACL repairs but who had not articular cartilage defects. At a mean follow-up of 6 years, there was little difference in symptom scores. This suggests that OA takes time to develop, though it should be noted that mean defect size in this cohort was only 1.7 cm^2.

Assumptions for modelling

For survival, we will use the Familiari et al[79] figures because they are based on a number of studies. (Note that these results are not as good as in some individual studies). Mean survivals;

87% at 5 years
79% at 10 years
73% at 15 years (range 56% to 84%, 5 studies)
68% at 20 years (range 66 to 69%, two studies)

One study[32] reported 59% survival at 25 years.

In the base case, we assume no one has TKR before age 55, so if OCA fails, they will have conservative symptomatic treatment till age 55. In practice some people may have TKR at age 50, whereas others might postpone it till age 60.

For the no-surgery arm, we assume that they have few symptoms for 10 years, on average, because there are two main groups, those with OCD in whom symptoms may not appear for many years, and those with chondral injuries with poor underlying bone structure, who present with pain. They will need conservative therapy till TKR at age 55, after which they become eligible for TKR.

From ages 40 to 55 they will have increasing disutility from OA. By about age 60, at least 60% will have had TKR. Whereas by age 60, only at most 22% of the OCA group will have had TKR, assuming that all graft failures do have TKR.

After failure of OCA, no matter when, we assumed that a second OCA would be offered, with 10-year survival poorer than after primary, but still around 50% at 10 years.

For cost purposes, we assumed fresh allografts (not cryopreserved as from National Tissue Bank) and we assumed that small lesions (under $2cm^2$) would not receive OCA, but would be treated by e.g. mosiacplasty (in line with the UK Surgeons Consensus document on ACI and the NICE guidance on ACI). In the base case, the cost of an allograft was taken from the JRF Ortho price list, as £12,850. (http://jrfortho.org/) . We used a lower cost in a sensitivity analysis.

OCA revisions

OCA repairs of osteochondral defects are usually successful, but a proportion fails as reported earlier. One option for these patients is another, revision OCA. There are few studies on revision OCA.

Horton et al[40] provide a study wherein all patients had revision of previous OCA. Some other studies include a few patients having revision OC (Emmerson 5 OCAs[56], Gortz 3[2], Levy 15[24], Meric 3[35]) after failed primary OCA, but do not give results of these separately, probably because of the small numbers.

So our best evidence on the success of second OCA after failure of the first OCA, comes from the small study by Horton, Bugbee et al from La Jolla, California.[40] Their series had 33 patients. Failure was defined at progression to partial or total TKA. The mean age at first OCA was 33 (range 16 to 64), at second OCAS 36, and failure of second OCA was at 5.5 years. Failure was commoner in older patients so mean age at failure was 45 years. All of the 13 failures had knee replacement (12 TKR, one PKR).

We assumed that revision OCA was less effective than primary OCA, but 61% got good results, and the alternative would have been continuing symptoms and conservative care, or arthroplasty at a much younger than ideal age.

Failure of revision OCA was linear over the first 12 years with survival at year 12 about 48%. So each year, 4% fail. After that, Horton et al had no failures but report some long-term survivals. Numbers by this stage are very small.

This study, though small and from a centre of excellence, is the best data we currently have on revision OCA. We can model the cost-effectiveness using the same model as for primary OCA, but applying different transition probabilities. However one problem is what to assume after year 12. One solution is that after year 12, we apply the same failure rates as in primary OCA of about 1.4 % per annum.

An alternative would be to assume no further failures (which is what Horton et al[40] reported), but that seems over-optimistic.

The results of this modelling must be treated with caution because of the small number of patients reported by Horton et al, but is the best we can do.

The aim of this analysis is to determine whether osteochondral allograft transplantation (OCA) is cost-effective compared to current standard practice (no OCA), as primary treatment for patients who have a defect both in the cartilage and the underlying bone.

Patients who have had OCA can have a number of outcomes:

- Permanent success – where symptoms are relieved, and no TKR is necessary;
- Failure, in the short-term treated symptomatically with analgesics; and in the medium-term developing osteoarthritis (OA) treated symptoms with conservative care (analgesics and physiotherapy); and in the longer-term have a knee replacement.

We have assumed a mean age at initial osteochondral injury of 30 years, that patients will develop symptomatic osteoarthritis around the age of 40, and might have a knee replacement later, but not until they are aged 55 years or above.

Model structure

A Markov model was developed within Microsoft Excel® and was considered the most appropriate to determine whether OCA would postpone or avoid knee replacement in the longer term for patients with a defect both in the articular cartilage and the underlying bone. The different health states for the model are shown by the ovals. The model shows all the transitions that can happen between the different health states by the direction of the arrows. The little loop arrows in the left hand corner of the ovals (recurring arrow) means that a patient can stay in that health state for more than one cycle, and perhaps indefinitely, until they die.

Figure 1 shows the model structure for patients who have no OCA transplantation (no OCA). The starting point of the model is patients aged 30 years. We have assumed that these patients manage their pain with analgesics. When they get to around the age of 40 years they begin to develop symptomatic OA, which they will manage with a conservative care package of analgesics and physiotherapy. When the patient turns 55 years of age, they may choose to have a knee replacement (see Figure 3). From all health states, patients can die.

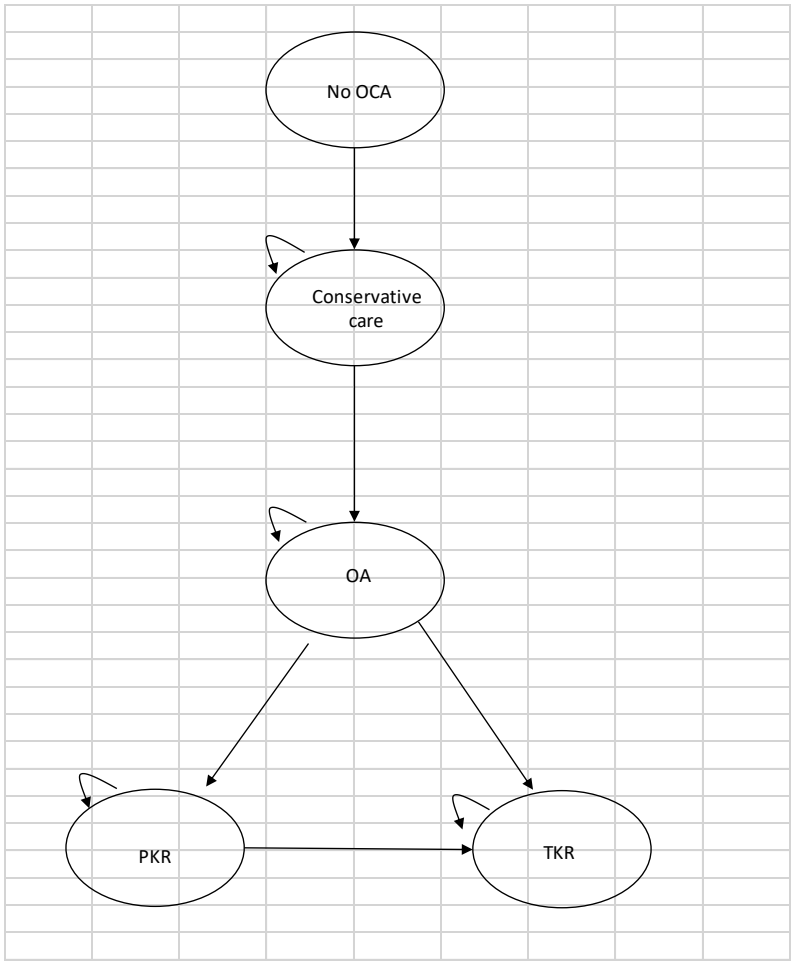

Figure 1: No OCA model structure

Figure 2 shows the model structure for patients who have an OCA transplantation. The starting point of the model is patients aged 30 years who have received an OCA transplantation. After the OCA, patients can then move either to a successful health state where symptoms are relieved or to failure health state where symptoms are not relieved. For those patients who move to the successful health state, some patients can remain there permanently, or over time the OCA can fail and they then move to the failure health state. We have assumed that these patients whose symptoms are not relieved, manage their pain with analgesics. When they get to around the age of 40 years they begin to develop symptomatic OA, so they will manage their OA symptoms with a conservative care package, which includes analgesics and physiotherapy. When the patient turns 55 years of age, they may choose to have a knee replacement (see Figure 3). From all health states, patients can die.

Patients over the age of 55 can have a knee replacement or conservative care. A patient can move to first knee replacement from the symptomatic OA health state when they reach the knee replacement age range (see Figure 3). The first knee replacement can be either a partial knee replacement (PKR) or total knee replacement (TKR), but all subsequent replacements are assumed to be TKRs. The first knee replacement can be a permanent or temporary success, so the patient moves to the successful first knee replacement health state, or the replacement can fail over time, so they move to the failure of first knee replacement health state, from which patients can choose to have another knee replacement or to have no further knee replacement. The second knee replacement

can be a permanent success, or a temporary success, and they move to the failure of further knee replacement health state, from which they can choose to have no further knee replacement and or to have another (3rd) knee replacement. Patients who move to the no further knee replacement health state, choose not to have another knee replacement and stay in this health state. From all health states patients, can die. From the knee replacement health states, there is a slight risk of mortality associated with the knee replacement.

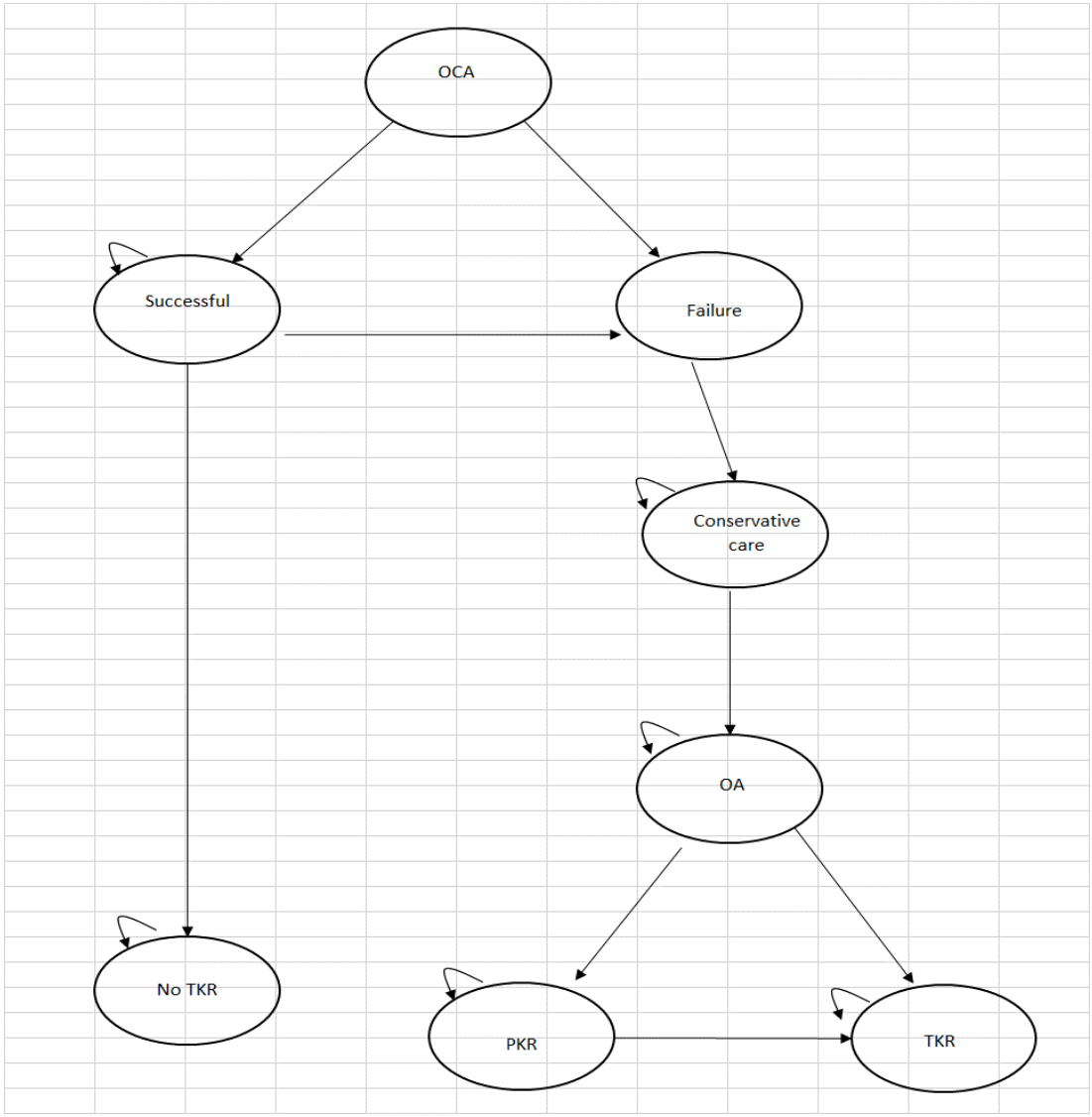

Figure 2: OCA model structure

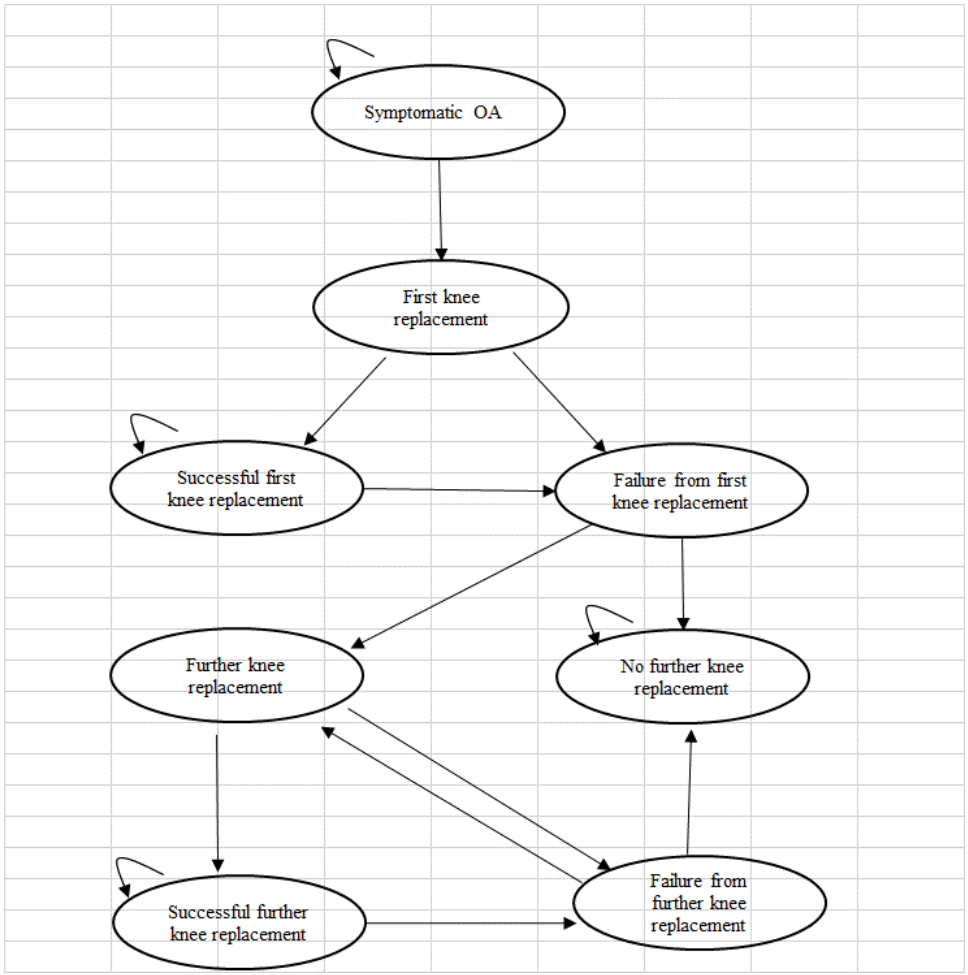

Figure 3: Model structure for knee replacement

Base-case analysis

For the base-case analysis, we have adopted a lifetime horizon (i.e. patients can live to 100 years) with a cycle length for the model set at one year and transitions between each health state occurring at the end of each cycle. A hypothetical cohort of a 1,000 patients with a defect both in the cartilage and the underlying bone with a starting age of 30 years are followed. We have not differentiated by gender. The analysis is conducted from the perspective of the UK National Health Service (NHS) and personal social services (PSS). All costs are in pounds sterling (£) in 2016/2017 prices. Health outcomes are measured in quality-adjusted life years (QALYs). Results are expressed as incremental cost per QALY gained. An annual discount rate of 3.5% is applied to both costs and outcomes in line with recommended guidelines.

Model inputs

Transition probabilities

For the base-case analysis, annual transition probabilities were based on data derived from the literature and assumptions from clinical experts. OCA survival (of allograft) was based on rates provided in the systematic review by Familiari et al.[79] The mean 5, 10, 15 and 20 year survival rates were: 86.7%, 78.7%, 72.8% and 67.5% respectively.[79] Longer-term graft survival was based on a study by Raz et al[32], who reported a 25 year survival rate of 59.0%. We fitted these points onto a graph to check the plausibility of the survival curve and then calculated annual transition probabilities from this survival curve to use in our economic model. Once they move out of the

successful health state and into the failure/conservative care/OA arm, we have assumed that patient will stay there until they get to the knee replacement age.

For the No OCA arm, patients remain in the conservative care/OA arm, until they get to the knee replacement age.

When the patient turns 55 years, we have assumed that 40% will remain in the OA health state, 30% have a PKR and 30% have a TKR.

Transition probabilities for success and failure for patients who needed knee replacements or knee replacement revisions were derived from two studies: Gerlier et al[80] and Dong and Buxton.[81]

Utilities

For patients who move to the following health states: successful health state or no TKR health state, we have used the utility values for the UK general population and adjusted this using an age-related utility decrement.[82]

For those patients who move to the failure/conservative care health state we have used a utility value of 0.721 which is based on non-obese patients who had knee pain and were aged between 25-44 years from Losina and colleagues[83]; the authors modelled different pharmacological regimens for knee osteoarthritis prevention.

For patients who developed osteoarthritis, we have used a utility value of 0.645 from Mari et a[84], which was based on patients who had knee osteoarthritis with a non-pharmacologic option (physical therapy).

Mean utility values are the same for knee replacements after OCA or no OCA and are based on utility values used in our previous report.[12] Before the first knee replacement (PKR or TKR), patients are assumed to have the same utility value (0.615). This value was based on an average of two utility values: 1) the EQ-5D index score at baseline pre-operatively for knee arthroplasty (0.51)[85] and 2) an estimate for TKR operation for knee problem (0.72).[81] For patients who move to the successful first TKR or PKR health state, a utility value of 0.780 was used.[81] This value was estimated from the generic Knee Society Score scale and was applied to the normal health state after primary TKR. If patients move to the successful further TKR health state we have assumed that they will have the same utility value as if it was a first TKR. Gerlier et al[80] was used to obtain two further utility values: 1) for patients for whom TKR has failed, and a further TKR is required, the value was based on the failed TKR/revision health state (0.557) and 2) for patients who move to the no further TKR health state value, this was based on patients who had no clinical success five years after surgery (0.691).

Resource use and costs

All unit costs are presented in pounds sterling (£) in 2016/17 prices. The cost of OCA transplantation includes the costs of the OCA (femoral condyle) graft and the implantation. The implantation cost was based on the costs for major knee procedures for non-trauma patients who are 19 years and older with a CC score 0-1 which was obtained from the NHS reference costs.[86] We have assumed that before a patient receives the OCA transplantation they have an outpatient appointment with an orthopaedic consultant. We have also added in a cost of three follow-up outpatient clinic visits as most patients are seen between 6 weeks and 3 months post-operation and also eight visits to see a hospital physiotherapist where each session lasts 30 minutes (see Table 4).

Table 4 Base-case mean costs used in the economic model

Resource use	Information	Unit cost (£)	Source
OCA			
Fresh OCA graft	Fresh OCA including implantation (HRG code: HN23C)	£15,560*	NHS reference costs 2015/16 + email
Outpatient visit	Consultant led outpatient first attendance (HRG code: WF01B)	£138.43*	NHS reference costs 2015/16
3 post-operation visit	Consultant led outpatient follow-up attendance (HRG code: WF01A) 8 hospital visits a year (30 mins each)	£335.89*	NHS reference costs 2015/16
Physiotherapy		£132.00	UCHSC 2017
Total cost		***£16,166.63***	
Non-operative package			
Paracetamol	1000mg, twice a day per year	£23.21	BNF 2016/17
Ibuprofen	Once a day per year	£12.47	BNF 2016/17
Physiotherapy	8 hospital visits a year (30 mins each)	£132.00	UCHSC 2017
Total cost per year		***£167.69***	
Knee replacement (KR)			
First TKR (PKR or TKR)	Very major knee procedures for non-trauma with CC score 0-1 (HRG code: HN22E)	£5,754.17*	NHS reference costs 2015/16
Further TKR	Second TKR	£13,551.05*	Clar et al (2005)
Outpatient visit	Consultant led outpatient FU attendance (HRG code: WF01A)	£111.96*	NHS reference costs 2015/16

* Uplifted to 2016/17 prices using the Hospital and Community Health Services (HCHS) index (UCHSC 2017)[87]

We have assumed patients with OA will receive conservative care consisting of analgesics, paracetamol and ibuprofen, and physiotherapy, eight visits to see a hospital physiotherapist where each session lasts 30 minutes. Medication costs where obtained from the British National Formulary.[88]

The cost for a first knee replacement, either a TKR or a PKR, was obtained from the NHS reference costs[86], using the same assumptions made in our previous work.[12] After a PKR, a second knee replacement would be a TKR, and we have assumed that this would cost £5,754. However, after a TKR, a subsequent TKR is almost double the cost, because the implants are more expensive and it is technically more difficult.[89] Any subsequent knee replacements would all be TKRs at a cost of £13,551. Based on clinical experiences, we have included in the first year after knee replacement (KR), the cost of two outpatient visits (see Table 4).[12]

We have assumed there would be no further costs after the first year if patients enter the successful health states.

Mortality

We used data from the UK general population lifetime tables for age-specific mortality rates [ONS, 2014], combining the average probability of death for men and women. As the cohort ages,

mortality rates generally increase throughout the model time horizon and patients can move to the dead state. Patients undergoing surgery for a PKR or TKR are subject to a risk of mortality. To reflect this higher mortality, rates were obtained from a study by Mahomed et al[90]. For patients undergoing a knee replacement or a knee revision, the mortality rates were reported as 0.7% and 1.1% respectively.[90]

Measuring cost-effectiveness

The base-case analysis assessed the cost-effectiveness of OCA compared with no OCA. For a cohort of a 1,000 patients we estimated their expected QALYs based on their likelihood of surviving each cycle, their expected health state utility values, and their expected costs. A lifetime horizon was adopted from a starting age of 30 years. The analysis is conducted from an NHS and PSS perspective. Costs are expressed in 2015-2016 prices in UK pounds sterling. The health outcome of interest was the QALY. We report the incremental cost-effectiveness ratio (ICER), measured as cost per QALY gained. Discount rates of 3.5% were applied to both future costs and outcomes.

Results

Table 4 below presents the base-case deterministic results when using an OCA graft price of £12,850. The results highlight even though OCA transplantation is more costly, it is also more effective than not having an OCA. The discounted cost per QALY (incremental cost-effectiveness ratio) is £4,692.

Table 4: Base-case deterministic cost-effectiveness results

Procedure	Total mean costs	Total mean QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY gained)
Deterministic - undiscounted					
No OCA	£11,369	37.11	-	-	-
OCA	£23,539	41.51	£12,170	4.40	£2,765
Deterministic - discounted					
No OCA	£4,828	17.68	-	-	-
OCA	£18,652	20.63	£13,824	2.94	£4,692

The key cost driver is the cost of the graft, but over the lifetime horizon, there are QALYs gained from using OCA, and there are cost savings to the NHS later due to fewer people in need of a TKR in the OCA arm.

Table 5 below presents the base-case deterministic results when using an OCA graft price of £3,892.50 (€4,174) based on costs in Spain. Even though OCA transplantation is slightly more costly, it provided more QALYs than not having an OCA. The discounted incremental cost-effectiveness ratio is £1,652.

Table 5: Deterministic cost-effectiveness results – changing the cost of the graft

Procedure	Total mean costs	Total mean QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY gained)

Deterministic - undiscounted					
No OCA	£11,369	37.11	-	-	-
OCA	£14,581	41.51	£3,212	4.40	£730
Deterministic - discounted					
No OCA	£4,828	17.68	-	-	-
OCA	£9,694	20.63	£4,867	2.94	£1,652

Sensitivity analyses

Table 6 below presents the deterministic results assuming that if people need a knee replacement they can have it at 45 years instead of 55 years as in our base-case model. This means that they have fewer years of symptoms and hence some QALY gain, but may have a higher TKR revision rate in later years. The results are in line with the base-case model - OCA is more costly but more effective than not having an OCA. The discounted incremental cost-effectiveness ratio is £5,084.

Table 6: Deterministic cost-effectiveness results – knee replacement at 45 years

Procedure	Total mean costs	Total mean QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY gained)
Deterministic - undiscounted					
No OCA	£10,891	38.20	-	-	-
OCA	£23,423	42.02	£12,532	3.82	£3,283
Deterministic - discounted					
No OCA	£5,629	18.24	-	-	-
OCA	£18,910	20.85	£13,282	2.61	£5,084

Table 7 below presents the deterministic results for revision OCA using data from Horton et al[45]. F or simplicity and because of the lack of data we have re-run the cost-effectiveness model using the probabilities of OCA revision as the primary OCA. Again results are in line with the base-case model – even though OCA is more costly, it is more effective than not having an OCA. The discounted incremental cost-effectiveness ratio is £6,760 (nearly £2,000 more than the base-case ICER). However by generally accepted costs per QALY, this is still very good value. Caveats are required. The study by Horton and colleagues is small, and comes from one of the world centres of excellence in OCA. But even if the ICER was trebled, it would still fall below the threshold used by NICE in the UK as a guide to value for money.

Table 7: Deterministic cost-effectiveness results – survival rates from Horton et al for second revision

Procedure	Total mean costs	Total mean QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY gained)
Deterministic – undiscounted					
No OCA	£11,369	37.11	-	-	-
OCA	£25,601	40.18	£14,231	3.07	£4,634
Deterministic – discounted					
No OCA	£4,828	17.68	-	-	-
OCA	£19,710	19.88	£14,882	2.20	£6,760

Conclusions

OCA appears highly cost-effective.

If a first OCA fails, a second, revision OCA also appears cost-effective, but this is based on only one small study.

2. Allografts in reconstruction of the anterior cruciate ligament

Summary

Reconstruction of the anterior cruciate ligament is highly successful whether with autografts or allografts. Autografts are nowadays most commonly from the hamstrings, but BPTB autografts may also be used.

Failures do occur but this does not necessarily mean that there was something wrong with the procedure or the technology. It should be borne in mind that people having these procedures do so because they have damaged or ruptured their own tissues, perhaps by putting great demands on the knee structures, often during sport.

Recent studies show little difference in failure rates between autografts and allografts (about 6% and 7% respectively). In cost-effectiveness analysis, the price differential is the main factor, making autografts the first choice.

However there will be situations, particularly in revision ACL reconstruction, where an allograft may be preferred, or may be the only reasonable option available.

Background

Our analysis is about reconstruction of the anterior cruciate ligament. We have not examined repair. Some people do try to repair the anterior cruciate ligament (ACL) by reconnecting the ends, but results do not so far seem to have been good, partly because the middle section has poor blood supply and does not heal well, partly because a complete rupture leaves a gap filled by synovial fluid.

The knee joint is one of the most complex in the body. It is mainly a hinge for flexion (bending the knee) and extension (straight leg) but also allows some rotation. The round ends of the femur, the condyles, rest on the relatively flat surface of the tibial condyles. This is unlike, for example, the ball and deeper socket nature of joints such as the hip, and so stability is maintained by ligaments and muscles. Forces transmitted across the knee joint are approximately two to three times body weight whilst walking.

The ACL runs from towards the front of the tibia, obliquely upwards and backwards to the inside of the back of the lateral femoral condyle. It prevents the femur from sliding too far back on the tibial surface and provides some rotational stability to the knee.

When viewed, the ACL appears as a helical structure, particularly when the knee is flexed. This is because the fibres originating most anteromedially (AM) insert posteriorly and proximally on the femoral condyle, whereas the fibres originating posterolaterally (PL) on the tibia insert anteriorly and distally on the femoral condyle. Whilst the ACL is a single structure morphologically, there are two functionally separate structures, named the AM and PL bundles. The AM bundle is tight in flexion and relatively relaxed in extension, whereas the PL bundle is tight in extension and relaxed in flexion. Therefore the PL bundle has more effect on stability when the knee is in extension and is thought to convey rotational stability.

ACL rupture can be managed conservatively. Physiotherapy can be useful. But most patients do better with reconstruction, and reconstruction has been reported to be cost-effective in competitive athletes [91]. In the ACL-deficient knee, instability is the primary problem. Some people cope when walking in straight lines, but cannot manage activities that involve pivoting or twisting (most team or

racket sports and some occupations). About a third of ACL-deficient people have troublesome instability in day-to-day life, often in minor turns or twists, but occasionally just walking.

Instability can be unpleasant or painful in itself, but is also associated with meniscal tears after major pivots.

Autografts can come from different source tendons. The commonest source now seems be hamstring tendons. An alternative is to use a piece of the patellar tendon with a piece of bone at each end – bone-patellar tendon-bone or BPTB. Some surgeons prefer BPTB as first line, and others use BPTB in high risk patients.

The three hamstring muscles are at the back of the thigh: biceps femoris, semitendinosus and semimembranosus. Their function is to flex the knee. The gracilis muscle along the medial side of the thigh also helps to flex the knee.

For hamstring autografts, the tendons of the two smallest muscles, the gracilis and the semitendinosus, are used in most cases. In some cases the semitendinosus alone may be used and quadrupled. The whole tendons are removed from within their sheath but sufficient power remains in the larger hamstring muscles for this not to cause problems in most sportspeople. There are a few reports of some reduction in knee flexion strength [92, 93] or maximum speed such as yards gained.[94]. Fear of repeat injury may be a limiting factor.[94] The tendons may partially re-grow. The other hamstring muscles may enlarge to compensate.

Once doubled, the combination of the gracilis and semitendinosus tendons is stronger than the BPTB autograft.[95] The Cochrane review of patellar versus hamstring autografts [92] reported more anterior knee problems and a statistically significant impairment in flexion range after PT autografts, compared with hamstring ones, but a more stable knee.

Prentice et al [96] reported practice in six registries, in Denmark, Luxembourg, Norway, the UK, Sweden and the USA, with data from 101,125 procedures (95% from Scandinavian countries, 4% from the UK). In Europe, allografts were used in only few patients (0.3 to 6.3%) whereas they were used in 40% in the US centres (Kaiser Permanente – KP). Revision rates by 7 years were reported for Norway (5.6%), Sweden (4.1%) and KP (6.1%).

A common source for allografts is the tibialis muscles. In a study by the MOON (Multicenter Orthopaedic Outcomes Network) group, tibialis tendons were the most used for allografts, though there was marked regional variation.[97] Around 90% of allografts used in the Midwest and West regions were from the tibialis, but none were used in the Northeast, where 55% were BPTB and 45% Achilles tendon. Hamstring tendons were rarely used, and not at all in some regions. The MOON group also reported the proportions of autografts and allografts, with little use of allografts in patients under 20, but much more in older patients, rising to 80% in the over-50s in one region.

Sheean and colleagues[98] advocate using the quadriceps tendon (between patella and rectus femoris) for autografts, either as tendon only or with a block of patellar bone. They note a shortage of head to head comparisons with BPTB grafts.

Wang and colleagues[99] report a non-randomised study in which 28 patients had a combined autograft and allograft and 20 had autograft alone. Result were better with autograft alone, but the allografts were irradiated.

Most allografts are from cadavers but there are several studies of allografts from living donors, in children and adolescents, with 98% from parents.[100] This form of allograft is outwith our remit so is not discussed further.

The advantages of allografts are no donor site morbidity, a shorter operation and less painful initial recovery. The disadvantages are slower graft incorporation and concern about higher rupture rates in some highly active groups, concern about disease transmission and increased cost. The concern about a higher re-rupture rate may not be warranted and may date from the time when allografts were irradiated, and weakened by that.

Particular concern has been expressed about using allografts in young (under 25) patients, but this concern may be unfounded. Brown and Carter[101] have reviewed the studies in young people, and note that some failures occurred in chemically treated or irradiated allografts, and that in other cases, patients tore grafts after returning to full sporting activities too early. They advocate preventing "exuberant return" too early, and also insisting on a strict rehabilitation programme with that prolonged if need be. Brown and Carter note studies that show higher failure rates in general in young active people, affecting both allografts and autografts. So failure in younger people may reflect activity rather than age.

Evidence – systematic reviews

We started by looking for recent good quality systematic reviews, then for any recent trials not included in those reviews. We identified a high quality, recent review of both systematic reviews and RCTs by Zeng et al 2016 comparing allografts and autografts in primary ACL reconstruction. We therefore started with that review[102] and only included primary studies that were published since the dates of its searches in 2014. For completeness, we examined eight other good quality recent systematic reviews. Two, Grassi[103] and Mohan[104], were reviews of revisions. Wasserstein 2015[105], Kan 2016[106] and Cvetanovich 2014[107] were reviews of primary ACLs. A review by Mascarenhas et al 2015[108] was a review of meta-analyses. Yao 2015[109] included only studies before 2014 so is not discussed further. Bansai 2017[110] was a good quality review but specifically on infections. It reported a much higher rate with HS autografts than with BPTB autografts, though this was based on observational studies, but no difference overall between autografts and allografts. Wei 2015[111] compared autografts with non-irradiated allografts. Park 2015[112] also focused on the irradiation issue and is discussed later.

The Wasserstein review[105] focused on primary ACL reconstruction, in patients < 25 years of age and highly active individuals (professional and college-level sports) and excluded studies of older patients or of mixed groups where the < 25 results were not provided separately. It is not clear how studies which included some older, highly active patients, were excluded but presumably they were excluded if results for the highly-active were not reported separately. Wasserstein and colleagues included one RCT and six cohort studies, four retrospective. Meta-analysis for risk of graft failure favoured autograft, although the review concluded that there was too little evidence to make strong conclusions. Their analysis showed no statistically significant difference between autografts and non-irradiated allografts – RR 0.57 – but numbers for that comparison were low and 95% CI wide, 0.57 to 2.27. The single RCT by Bottoni et al[113] reported an unusually high (non-irradiated) allograft failure rate of 26.5% compared to 8% with autografts.

Wasserstein et al did not include a study by Gee et al [114] who compared results of allograft ACL reconstruction in two groups of patients, one over 40 years and the other 25 year or under. Their focus was on outcomes in the older group, but they report the failure rate in the younger group

after 5 years was only 6.3%. The results in the over 40s were similar to those in the <25s, except for a higher prevalence of OA.

Cvetanovich et al[107] from Rush University did not include BPTB studies, such as Gorschewsky 2005[115], and the two Sun 2009 studies [116, 117]. Bi 2013[118] would have been excluded because it was in Chinese not English. The dates of the searches by Cvetanovich et al are not provided – they may have been before Bi was published. The review concluded that there was no statistically significant difference in outcome between autograft and allograft.

Kan et al[106] also compared autograft with allograft in primary ACL reconstruction. Eleven studies were included and autografts were shown to be superior to irradiated allografts but there were no significant differences between autograft and non-irradiated allograft.

Mascarenhas et al[108] from the Rush University group also provide a review of meta-analyses of allografts versus autografts, and conclude that the best evidence shows no differences in the key clinical outcomes and in particular rupture rates.

Revision ACL reconstruction

Two systematic reviews considered revision ACL, but with different purposes. Both carried out literature searches in 2016, and both included studies with at least two years of follow-up. Grassi et al[103] focused on the type of graft, and included 32 studies in a meta-analysis. Seven studies [111, 112,113,117, 118,124,125] used only allografts, two [120,121] used both BPTB allografts and autografts. When compared with any allograft type (irradiated or non-irradiated) outcomes generally favoured autograft, but when irradiated allografts were excluded the results were no longer statistically significantly different.

The focus of the review by Mohan et al[104] was on revision versus primary ACL reconstruction and they initially pooled studies of autograft and allograft. Similar failure rates between autograft (4.1%) and allograft (3.6%) were seen. However they include only two allograft studies, the Muliticenter ACL Revision Study Group (MARS) 2014 [115] and Kvist 2014. [119] Neither of those studies was included in the Grassi review. The MARS 2014 study was identified by Grassi et al but appears to have been excluded because results with irradiated and non-irradiated grafts were not separately reported. Over half were irradiated. The Kvist study appears to have been missed by Grassi et al because their search strategy required the word “failure”.

Table 8 shows the studies in the two reviews.

Table 8: Studies of allografts in the Grassi and Mohan reviews

	Grassi 2017[103]	Mohan 2018[104]
Buda 2013[119]	X	
Chougule 2015[120]	X	
Fox 2004[121]	X	
MARS Group 2014[122]		X
Johnson 1996[123]	X	
Kievit 2013[124]	X	
Kvist 2014[125]		X
Mayr 2012[126]	X	
Noyes 1996[127]	X	
Pascual-Garrido 2014[128]	X	
Ra 2013[129]	X	

Since those reviews, some new evidence on revision ACLR has been published. The MARS group 2017[130] reported that 11% of 1205 patients had had further surgery by two years after revision ACLR, but only 19% of the reoperations were further revision ACLR. Note that over half the ACL grafts had been irradiated. The commonest procedures were meniscal (mainly meniscectomy) 27% and cartilage procedures (17%). Patients under age 20 had twice the odds of a further procedure compared to those 20 to 29.

Mitchell and colleagues[131] compared patients having primary and revision ACLR. They found no differences in age, gender, prevalence of meniscal tears, or allograft versus autografts. Patients having revisions had increased medial tibial slopes, which has been found to be a risk factor for ACL graft failure in other studies[132] presumably due to changes in the biomechanics of the knee.

The quality assessment for the reviews is shown in Table 9 and their results and conclusions in Table 10.

ACLs

Table 9: Quality assessment of ACL reviews using NIH criteria

Review	Focused question	Eligibility criteria	Searches	Dual review	Validity	Study details	Publication bias	Heterogeneity
ACL								
Zeng et al 2016[102]	Y	y	y	y	y	y	Y	Y
Mascarenhas et al 2015[108]	Y	Y	Y	Y	Y	Y (reviews)	N	Y
Wasserstein et al 2015[105]	Y	Y	Y	Y	Y	Y	Y	Y
Cvetanovich et al 2014[107]	Y	Y	Y	Y	Y	Y	N	Y
Roberson et al 2017[133]	Y	Partial	Y	?	N	Y	N	N
Park et al 2015[112]	Y	Y	Y	?	N	Y	N	Partial
Bansal et al 2017[110]	Y	y	y	y	y	y	y	Y
Wei et al 2015[111]	Y	y	y	y	y	y	y	y
Yao et al 2015[109]	Y	y	y	y	y	y	n	y
Kan et al 2016[106]	Y	y	y	y	y	y	y	y
Revision ACLs								
Grassi et al 2017[103]	Y	Y	Y	Y	N	Y	N	N
Mohan et al 2017[104]	Y	Y	Y	Y	Y	Y	N	Y

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported

1. Is the review based on a focused question that is adequately formulated and described?
2. Were eligibility criteria for included and excluded studies predefined and specified?
3. Did the literature search strategy use a comprehensive, systematic approach?
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?
5. Was the quality of each included study rated?
6. Were the included studies listed along with important characteristics and results of each study?

Zeng et al 2016[102] reviewed systematic reviews and RCTs comparing allografts and autografts in people having primary ACL reconstruction. The review of reviews included 10 systematic reviews and nine RCTs. The review was assessed as very high quality (8 of 8 quality items rated as 'yes'). Autograft versus allograft (some of which used radiated grafts) had a pooled risk ratio on the overall IKDC level 'normal and nearly normal' of 1.03 (95% CI 1.00, 1.07); p=0.03, in favour of autograft. There was no statistical heterogeneity (I^2 0%). However, when two studies were excluded in sensitivity analyses (the review examined single study influence on results by removing one at a time) the pooled RR was no longer statistically significant. Clinical failure was also less frequent (RR, 0.47; 95% CI: 0.31, 0.73; P =0.0007; I^2 23%), and Tegner scores (WMD, 0.36; 95% CI: 0.11, 0.60;

P=0.004; I^2 0%) differences were also statistically significant, but the Lysholm score was not (WMD, 0.02; 95% CI: -0.71, 0.75; P=0.96; I^2 44%). These analyses included studies using irradiated allografts. Subgroup analyses of autograft versus non-irradiated allografts were also reported for these outcomes, none of which were statistically significant (Lysholm WMD, -0.64; 95% CI: -1.45, 0.17; P=0.12; I^2 0%; Tegner WMD 0.16; 95% CI: -0.16, 0.47; P=0.34; I^2 0%). The authors concluded that autograft had advantages over irradiated allograft with respect to function and stability, whereas there were no significant differences between autograft and non-irradiated allografts.

We note that a protocol for a Cochrane review of allografts versus autograft for ACL reconstruction was published in 2013, but the Cochrane Review Group website reports that this review has been discontinued due to lack of progress.[134]

We identified another 2017 review by Pujji and colleagues[135] but it included only two trials (Bottini 2015[113] and Jia 2015[136]) and the Mariscalco 2014 review[137] and was not included. Mariscalco et al [138] included nine studies comparing autografts with non-irradiated allografts, four of which were RCTs or mainly RCT (one trial had 25% patient choice and 75% randomised), with the other studies mainly patient choice. They found no difference in outcomes.

Table 10: Results and conclusions of reviews of ACL reconstruction

Results	Conclusions
Zeng et al 2016[102] Aim to compare autograft with allograft in anterior cruciate ligament reconstruction; review of RCTs and review of reviews.	
Mean follow-up > 24 months Favoured autograft: Overall IKDC level (RR for normal and nearly normal, 1.03; 95% CI, 1.00 to 1.07; P=0.03; I^2 0%) Clinical failure (RR, 0.47; 95% CI, 0.31 to 0.73; P=0.0007; I^2 23%) Lachman test (RR, 1.18; 95% CI, 1.02 to 1.36; P=0.03; I^2 71%) Instrumented laxity test (WMD, -0.88; 95% CI, -1.47 to -0.28; P=0.004; I^2 90% Tegner score (WMD, 0.36; 95% CI, 0.11 to 0.60; P=0.004; I^2 0%) Sensitivity analyses suggested that the difference in overall IKDC level appeared to be nonsignificant when two studies with different methods were excluded. No differences between autograft and allograft groups: Lysholm score (WMD, 0.02; 95% CI, -0.71 to 0.75; P=0.96; I^2 44%) Pivot-shift test (RR for normal [level 0], 1.05; 95% CI, 0.99 to 1.13; P=0.12; I^2 57%) Daniel 1-leg hop test (RR for normal and nearly normal, 0.99; 95% CI, 0.91 to 1.07; P=0.74; I^2 71%) Sensitivity analyses indicated that the exclusion of 2 studies with different methods suggested good consistency among the remaining studies	Autograft had advantages over irradiated allograft with respect to function and stability, but there were no significant differences between autograft and non-irradiated allograft.
Mascarenhas et al 2015[108] Aim to conduct a systematic review of meta-analyses comparing anterior cruciate ligament reconstruction with autografts and allografts to examine discordance and to determine which meta-analyses provide the current best evidence	
All studies included in this review were in the more recently published review by Zeng and therefore no results have been extracted.	The current evidence suggests no differences in rupture rates and clinical outcomes.

Wasserstein et al 2015[105] Aim was to determine whether there is a difference in failure prevalence between allograft and autograft ACLR in young and highly active patients	
Mean follow-up ranged from 24-51 months in the 4 studies that reported follow-up. Graft failure prevalence across all patients (autografts and allografts) was 13.9% (133/1016). The pooled graft failure prevalence for patients undergoing QHS autograft, BPTB autograft, and allograft was 9.5% (44/463), 9.8% (32/325), and 25.0% (57/228), respectively. The combined failure prevalence of all autografts was 9.6% (76/788). Meta-analysis of all 7 studies for overall risk of graft failure RR, 0.36; 95% CI, 0.24-0.53; P<0.00001; I^2 16% (favouring autograft). Meta-analysis of 3 studies for postoperative Lysholm scores mean difference 1.87, 95% CI -0.44, 4.18, p<0.11, I^2 21% No formal meta-analysis could be undertaken on Tegner activity scale, IKDC, SANE or Cincinnati score (says no individual study reported significant outcomes) Subgroup analyses of irradiated versus non-irradiated allografts and autografts.	The overall failure rate in these young patients was higher with allografts. Wasserstein and colleagues felt there was a lack of data in this patient group as to whether the difference between autografts and allografts was related to allograft sterilisation methods. They reported a significant advantage of autografts over irradiated allografts, but no difference between autografts and non-irradiated allografts. However the advised caution due to the small number of studies that used irradiated grafts.
Cvetanovich et al 2014[107] Aim was to review the published literature to compare outcomes of ACL reconstruction with hamstring autograft versus soft-tissue allograft. Studies of BPTB grafts were excluded.	
Allografts came from hamstrings in three trials, and tibialis anterior and Achilles tendons in one trial each. All but one used fresh frozen allografts. One used irradiated hamstring. Mean follow-up period 47.4 months (SD 26.9). Two studies reported operative time longer with autografts – means of 77 and 60 minutes Lysholm score (RR, -0.07; 95%CI, 0.28 to 0.15; P= 0.53, I^2 0%) Tegner score (RR, 0.11; 95% CI, -0.15 to 0.36; P=0.40, I^2 23%) IKDC normal or nearly normal (RR, 1.01; 95% CI, 0.96 to 1.05; P=0.8, I^2 0%)	No statistically significant difference in outcome in ACL reconstruction with hamstring autograft and various allografts. Cvetanovich et al comment on the poor quality of primary studies.

Reoperations (RR, 1.14; 95% CI, 0.40 to 3.25; P=0.8, I^2 0%). Lachman test negative (RR, 1.37; 95% CI, 0.88 to 2.14; P=0.16, I^2 86%) Pivot-shift test negative (RR, 1.05; 95%CI, 0.92 to 1.20; P=0.46, I^2 63%) KT arthrometer testing <3mm (RR, 1.11; 95% CI, 0.89 to 1.39; P=0.36, I^2 83%) Sensitivity analysis of one heterogeneous study did not affect results.	
Wei et al 2015[111] To compare autograft with non-irradiated allograft primary for reconstruction of anterior cruciate ligament.	
Mean follow-up not reported, (individual study follow-ups reported) Lysholm score, 4 studies: MD -1.46 (95% CI -2.46, -0.47), p=0.004, I^2 0% (favours allograft) Subjective IKDC, 4 studies: MD 0.61 (95% CI -0.75, 1.97), p=0.38, I^2 0% Tegner score, 4 studies: MD -0.02 (95% CI-0.20, 0.15), p=0.80, I^2 0% Complications, 10 studies: RR 1.21 (95% CI 0.74, 1.98), p=0.44, I^2 58% Sensitivity analyses excluded 5 studies not clearly indicated as irradiated.	Autografts showed no advantage over non-irradiated allograft. One outcome favoured allograft.
Bansal et al 2017[110] Aim was to compare the incidence of infections after ACL reconstruction with autografts compared with allografts.	
Mean follow-up of studies of allografts ranged from 3 – 93.6 months No significant difference in the incidence of infections after ACL reconstruction with autografts compared with allografts (RR, 1.035; 95% CI, 0.589, 1.819), I2 0%.	This review and meta-analysis found a significantly lower risk of infection using BPTB autografts compared with hamstring autografts and no significant difference in the incidence of infections using autografts compared with allografts. However about half the studies had no infections in either group, and were excluded, and the meta-analysis was dominated by two large studies from the Kaiser Permanente group (Maletis) and the mOOn knee group (Brophy).
Kan 2016[106] Aim was to compare autografts and allografts in ACL reconstruction	

13 studies included. Mean follow-up not reported. Clinical failure, 11 studies, RR 0.42, 95% CI 0.28, 0.63, P<0.0001; I2=0%, favours autograft Tegner score, MD 0.26, 95% CI 0.06, 0.45, P=0.01; I2=0%, favours autograft Lysholm score, MD 0.27, 95% CI -0.79 to 1.32, P= 0.62; I2=59% subjective IKDC score, MD 1.51, 95% CI -0.13 to 3.14, P=0.07, I2=72% Subgroup analyses: Autograft performed better in clinical failure, Lysholm score, Tegner score and subjective IKDC score than irradiated allograft and no significant differences were found between autograft and nonirradiated allograft.	The main conclusions were that autografts were superior to irradiated allografts but not to non-irradiated allografts
Yao et al 2015 [109] to compare the clinical results of bone–patellar tendon–bone (BPTB) autograft and BPTB allograft in primary anterior cruciate ligament reconstruction. (primary ACLs)	
Mean follow-up not reported Lysholm score, 6 studies, WMD 1.57 (95% CI -1.09, 4.24), p=0.25, heterogeneity p=0.03 Tegner score, 7 studies, WMD 0.33 (95% CI -0.05, 0.71), p=0.09, heterogeneity p=0.01 Failure, 9 studies, OR 0.31 (95% CI 0.13, 0.78), p=0.01, heterogeneity p=0.61 Subgroup analysis on fresh-frozen allograft and irradiated allograft: in fresh-frozen subgroup significant difference (WMD = 0.38, 95 % CI 0.11, 0.65, p = 0.006) in Tegner scores was found between autograft and allograft under the fixed-effect model.	Overall, BPTB autograft had a significantly lower rate of failure than BPTB allograft, but subgroup analysis excluding irradiated grafts showed no difference. Patients returned to sport earlier after BPTB autograft than after fresh-frozen BPTB allograft. The authors concluded that the current evidence base was inadequate to identify which graft is better.
Roberson et al 2017[133] Aim to assess the proprietary processes of allograft tissues and their clinical outcomes and biomechanical properties (not stated if primary or revision ACLs included, discusses both in the introduction, focus of review was on processing of the allografts).	
No meta-analysis or pooling of results were reported.	The authors conclude that comparison of processing methods is difficult, with little difference except for a high failure rate with the Tutoplast process.
Park et al 2015[112]	

Aim was to determine the clinical implications of using allografts treated with different tissue-processing techniques in primary ACLR surgery (primary ACLs)	
Mean follow-up 49.8 months (range 12-170) Significant difference between non-irradiated and irradiated: Lysholm scores non-irradiated pooled weighted mean 89.8 (95% CI, 87.8-91.8) versus irradiated pooled weighted mean 84.4 (95% CI, 79.0-89.8), p<0.05 (WMD 95% CI 0.7-10.1). IKDC grade A or B (all studies) non-irradiated weighted proportion 0.86 (95% CI, 0.80-0.93) versus irradiated 0.91 (95% CI, 0.88-0.94), p<0.05 (proportion difference 95% CI –0.09, –0.01). See below for sensitivity analysis Graft complications non-irradiated weighted proportion 0.0136 (95% CI, 0.0006-0.0266) versus irradiated 0.0012 (95% CI, –0.0067 to 0.0091), p=0.0498 (proportion difference 95% CI 0.0040-0.0228) Revision surgery non-irradiated weighted proportion 0.0022 (95% CI, –0.0033 to 0.0077) versus irradiated 0.0250 (95% CI, –0.0011 to 0.0511), p<0.001 (95% CI –0.0420 to 0.0057). Non-significant difference between non-irradiated and irradiated: Tegner scores, non-irradiated pooled weighted mean 6.4 (95% CI, 5.4-7.4) versus irradiated pooled weighted mean 5.9 (95% CI, 3.3-8.5), p>0.05 (WMD 95% CI –1.8 to 2.8). IKDC grade A or B (removing 1 outlier) non-irradiated 0.89 (95% CI, 0.85-0.94) versus irradiated 0.91 (95% CI, 0.88-0.94), p>0.05 (proportion difference 95% CI –0.06 to 0.02).	Park et al concluded that primary ACLR using non-irradiated fresh-frozen allografts provide better clinical outcomes than those using low-dose (<2.5 Mrad) irradiated grafts. They reported that there were insufficient data for comparisons of fresh-frozen with freeze-dried and cryopreserved grafts.
Revision ACLs	
Grassi et al 2017[103] To perform a meta-analysis of the outcomes of revision anterior cruciate ligament (ACL) reconstruction, comparing the use of different types of graft. (revision ACLs)	
Results: Mean follow-up was 5.4 years (range 2.0 to 9.6) for those treated with autografts, and 4.0 years (range 2.3 to 6.0) for those treated with allografts. Allograft were better than autografts on: mean Lysholm (OR 1.41 95% CI 1.07, 1.87) Tegner activity scores (OR 2.56 95% CI 1.64, 4.02) Autografts were better than allografts on: Complications (OR 2.92 95% CI 1.89, 4.50) Re-operations (OR 3.42 95% CI 2.34, 5.01)	Overall, autografts gave better results than allografts in revision ACL reconstruction, with lower post-operative laxity and rates of complications and re-operations. However once irradiated allografts were excluded, the outcomes of allografts and autografts were similar.

Subgroups: those with non-irradiated allografts had a significantly smaller rate of re-operation compared with autografts and tegner activity scores were higher. There was no significant difference in Lysholm score or complications between non-irradiated allografts and autografts (ORs not extracted)	
Mohan et al 2017[104] To determine overall objective graft failure rate, failure rate by graft type (allograft vs autograft reconstruction), instrumented laxity, and patient outcome scores following revision anterior cruciate ligament (ACL) reconstruction (revision ACLs)	
Results: mean follow-up was 57 months Overall objective failure rate: 6% (95% CI, 1.8%-12.3%) 8 studies pooled Mean IKDC subjective score: 76.99 (95% CI, 76.64-77.34), 2 studies pooled Mean KOOS symptoms score: 76.73 (95% CI, 75.85-77.61), 3 studies pooled Mean Lysholm score: 86.18 (95% CI, 79.08-93.28), 3 studies pooled	Failure rates were 4.1% for autograft reconstructions and 3.6% with allografts. However none of the included studies were RCTs, and there were only two allograft studies. Mohan et al also note graft failures rates falling over time with highest rates in the earliest (1996 to 2004) studies.

One of the primary studies, Gorschewski et al 2005 [115] reported an unusually high failure rate with BPTB allografts, with failures in 21% at 2 years and 45% by 6 years in the allograft group, compared to 5% and 6% in the autograft group. The allografts were treated with the Tutoplast methods and were irradiated.

Evidence – selected primary studies

We added 10 recent prospective studies of allografts in anterior cruciate ligament (ACL) reconstruction that were not in the reviews (Table 11). There were eight randomised controlled trials (RCTs), one cohort study and one case series. Study characteristics and baseline characteristics of the participants are summarised below (Table 12). The comparisons in five of the studies were not relevant to the primary question in this review.[139-143] The risk of selection bias in the RCTs was unclear in all but one study, Jia et al 2015,[136] which was considered to have a low risk. The quality of the non-randomised studies was fair. The overall quality of each study is reported within the results below.

Table 11: Prospective ACL studies included in this review

Author	Intervention details	Study Design
Studies comparing allografts and autografts		
Yoo et al, 2017[144]	ACL non-iradiated tibialis allograft vs HS autograft	RCT
Tian et al, 2016[145]	ACL irradiated HS allograft vs HS autograft	RCT
Bottoni et al, 2015[113] 2014[146]	ACL tibialis posterior non-irradiated allograft vs HS autograft	RCT
Jia et al, 2015[136]	ACL BPTB non-irradiated allograft vs HS autograft	RCT
Yang et al, 2017[147]	ACL HS non-irradiated allograft vs HS autograft	Cohort study
Other studies		
Tian et al, 2017[139]	ACL non-irradiated HS allograft vs irradiated HS allograft	RCT
Dai et al, 2016[140]	ACL allograft (hamstring versus bone-patellar tendon-bone). No irradiation mentioned	RCT
Niu et al, 2016[141]	ACL allograft (DBPTP vs 4SHS) non-irradiated	RCT
Kang et al, 2015[142]	ACL Allograft (single bundle BPTB vs double bundle tibialis anterior). No irradiation mentioned	RCT

Niu et al, 2017[143]	ACL Allograft (monolayer vs double layer). No irradiation mentioned.	Case series (comparison not relevant to review)

Prospective studies - Allografts versus Autografts

Four RCTs and one cohort study compared allograft with autograft for primary ACL reconstruction (Yoo 2017[144] ; Tian 2016[145] ; Bottoni 2015[113]; Jia 2015[136]; Yang 2017[147]). These had a total of 678 participants (approximately 337 allocated to allograft, 342 allocated to autograft, not all studies reported numbers of people allocated and the numbers actually analysed were lower in three of the studies). Mean length of follow-up ranged from 2.5 years to 10.5 years. Three studies were conducted in China, one in the USA, and one in South Korea. Eligibility criteria or indication for the allograft differed between the studies, see Table 12. In four studies between 15% and 60% of participants had concurrent procedures; it was not clear from the reporting of the remaining study if concurrent procedures were undertaken (Table 12). Mean age was 24-33 years across the studies, and the majority of participants were men in all but one study (Jia 2015[136] which had approximately 50% male). Details are given in Table 12.

The Tian 2016 study[145] used fresh-frozen allografts. The same group carried out a trial[148] using irradiated (2.5Mrad) allografts but found an increase in laxity with them, compared to autografts, and advised against their use. We have not included this trial.

Jia 2015[136] did not use irradiation.

Table 12: Study and baseline characteristics ACL reconstruction studies

Study	Indication / inclusion criteria	Concomitant procedures	Baselines
Comparative studies of allografts versus autografts.			
Yoo et al, 2017[144] **Country:** South Korea **Design:** RCT **Follow-up:** allograft 34.5 months (range, 25.3–59.5); autograft 32.8 months (range 28.7–52.1) **Sample size:** 141 (allograft 70, autograft 71)	Patients with ACL injury, with or without meniscal injury. 2008-2011. Minimum 2 years follow-up.	Meniscal repair or meniscectomy where required (approximately 60%).	**Age[a] :** allograft 24 (range 13-52); autograft 30 (range 15-62) **% male:** allograft 92.2%; autograft 89.7%
Tian et al, 2016[145] **Country:** China **Study design:** RCT **Follow-up duration**: total group 4.6 (4.0-5.5) years **Sample size:** 157 (allograft 79; autograft 78)	Scheduled for primary unilateral reconstruction of the ACL with no open physes, no severe arthritic changes in the knee, no previous injury or surgery on the affected knee, no multiple ligamentous injuries, no malalignment, not a revision reconstruction. 2010-2011	In the allograft group 16.9% and 35.6% also had repair or partial meniscectomy respectively and 13.6% had cartilage debridement; in the autograft these rates were 19.4%, 32.3% and 14.5% respectively (%s reported were based on those included in the analysis).	**Age[a] :** allograft 29.9 (6.1); autograft 30.5 (4) **% male:** allograft 81.4%; autograft 77.4%
Bottoni et al, 2015[113] **Country:** USA, active military population **Study design:** RCT (sealed envelopes) **Follow-up duration**: mean 126 months, range 120-132) **Sample size:** total 99 (100 knees); allograft n unclear (50 knees); autograft n unclear (50 knees). N participants do not add up.	≥18 years, symptomatic ACL deficiency, confirmed by MRI. 2002-2003.	Additional procedures included meniscal repairs (allograft 14.6 medial; autograft 14.6% medial; 6.3% lateral) and subchondral microfracture (allograft 6.3%; autograft 14.6%).	**Age[a] :** allograft 29.2 (5.5); autograft 28.9 (5.8) **% male:** allograft 87.8%; autograft 85.4%
Jia et al, 2015[136] **Country:** China **Study design:** RCT **Follow-up duration**: mean 81 months (range 28-86) **Sample size**: total 106; allograft 53; autograft 53	ACL tear, normal alignment, normal contralateral knee, and willingness to join the rehabilitation program. 2002-2011.	Rehabilitation for 4-6 months.	**Age[a] :** allograft 28 (range 18-36); autograft 31 (19-51) **% male:** allograft 49.1%; autograft 52.8%
Yang et al, 2017[147] **Country:** China	Age 16-55 years, primary unilateral ACL tear diagnosed by physical examination and MRI	Meniscus tear repair, meniscectomy (approximately 50%).	**Age[a] :** allograft 30.2 (8.9); autograft 32.6 (9.0)

Study design: Cohort study **Follow-up duration**: mean 2.5 years (range 1-5.5). **Sample size:** 175 (allograft 85; autograft 90)	and confirmed by arthroscopy, patients could have concomitant meniscus tears. 2008-2011		**% male:** allograft 60%; autograft 64.4%
Other studies			
Tian et al, 2017[139] **Country:** China **Study design:** RCT of irradiated versus non-irradiated hamstring allografts **Follow-up duration**: mean 5.7 years (range 5.0-6.5) **Sample size**: 112 (non-irradiated 56, irradiated 56)	Primary unilateral reconstructions of the ACL; no open physes present, no severe arthritic changes in the knee with Kellgren–Lawrence classification < grade 2, no previous injury or surgery on affected knee, no multiple ligamentous injuries, no malalignment, not a revision reconstruction. 2009-2010.	Concurrent procedures at surgery not reported.	**Age[a] :** non-irradiated graft 30.2 (5.6); irradiated graft 29.8 (6.1) **% male:** non-irradiated graft 79.5%; irradiated graft 79.5%
Dai et al, 2016[140] **Country:** China **Study design:** RCT of single bundle ACLR comparing 6-strand hamstring and BPTB allografts **Follow-up duration**: mean 52 months (range 30–68 months) **Sample size**: 129 (hamstring allograft 69, BPTB allograft 60.	Established diagnosis of ACL rupture, age 17-50 years. 2007-2009.	Not reported but states 'meniscal or chondral pathology was addressed as necessary'.	**Age[a] :** hamstring allograft 30 (6); BPTB allograft 29 (5) **% male:** hamstring allograft 59%; BPTB allograft 67.3%
Niu et al, 2016[141] **Country:** China **Study design:** RCT of double-layer BPTB and 4-strand hamstring allografts **Follow-up duration**: mean 40 months (range 36 to 48). **Sample size:** 110 (55 DBPTB allograft, 55 4SHS allograft)	No history of previous surgery on the injured knee; no concomitant injury of the other ligaments of the knee; a healthy contralateral knee; chondral lesions no worse than Grade II according to the Outerbridge classification; no meniscus repair or partial meniscectomy that involved more than one-third of the entire meniscus. 2010-2011	46% had partial resection or repair of the meniscus. No surgical interventions required for articular cartilage lesions.	**Age[a] :** DBPTB allograft 26 (5); 4SHS allograft 27 (4) **% male:** DBPTB allograft 50%; 4SHS allograft 52.9%
Kang et al, 2015[142] **Country:** China **Study design:** RCT of single bundle patellar tendon versus double bundle tibialis anterior allografts	ACL tear, no history of previous surgery in the injured knee; no concomitant injury of other knee ligaments; a healthy contralateral knee; chondral lesions no severer than grade II Outerbridge	Meniscal surgeries in 53% and 44% in the two groups respectively. Rehabilitation protocol for both groups.	**Age[a] :** SB allograft 30 (5); DB allograft 28 (5) **% male:** SB allograft 46.5%; DB allograft 51.2%

Follow-up duration: SB 31 (SD 5) months; DB 33 (SD 6) months **Sample size:** total 94, groups not stated.	classification; meniscus repair or partial meniscectomy involving < 1/3 of the entire meniscus; no patellofemoral symptoms or absence of systemic illnesses. Minimum 2 year follow-up. 2010-2011.		
Niu et al, 2017[143] **Country:** China **Study design:** case series comparing double versus single layer BPTB allografts. **Follow-up duration**: Minimum 4 years, DBPTB 52 (SD 4) months, BPTB 54 (2) months **Sample size:** 98 (47 DBPTB, 51 BPTB)	No history of previous surgery on the injured knee; no concomitant injury to other ligaments in that knee; a healthy contralateral knee; chondral lesions ≤ Outerbridge classification grade II prior meniscus repair or partial meniscectomy that involved less than one-third of the entire meniscus. 2010-2011	Meniscal repairs or resection (32 [32.7%]).	**Age**[a] **:** DBPTB allograft 24 (5); BPTB allograft 25 (4) **% male:** DBPTBB allograft 48.9%; BPTB allograft 52.9%

[a]mean (SD) unless stated otherwise

4SHS: four-strand hamstring; BPTB: bone-patellar tendon-bone; DB: Double bundle; DBPTB double-layer bone–patellar tendon–bone; SB: Single Bundle

Results – Failure and revisions, allografts versus autografts

Three studies reported failures and revision rates between allografts and autograft ACL reconstructions. In the RCT by Yoo 2017[144] at 33-35 months follow-up, the rates of revision were similar between groups (allografts 1.6%; autografts 1.5%). The rate of failure requiring revision was statistically significantly higher in the allograft group of the Bottoni 2015[113] RCT than the autograft group (26.5% and 8.3% respectively, p=0.03, duration of follow-up 10.5 years). In the third study by Yang et al 2017 [147], the failure rates at 2.5 years were 2.4% with allografts and 2.2% autograft. All three studies used fresh frozen non-irradiated allografts.

The reasons for the higher failure rate in Bottoni 2015 are not clear. The operations were done a long time ago, perhaps at a time when processing methods were more damaging. Grafts came from a single tissue bank over a relatively short period of time.

Results – progression of osteoarthritis

Outcomes related to progression of osteoarthritis (OA) were reported in two of the comparative studies. There were no statistically significant differences between allograft and autograft in these RCTs by Yoo et al 2017 and Tian et al 2016 (Yoo 2017[144] 6.25% versus 7.35% at 33-35 months follow-up; Tian 2016[145] 11.9% versus 11.3% at 4.6 years follow-up, allografts versus autografts respectively).

Results – Functional outcomes

Four of the studies reported the Lysholm knee score (Table 13) as an outcome although only two studies reported baseline and end-point values. Three of these were RCTs and one a cohort study. The risk of selection bias was unclear in all but the Jia 2015[136] study (which had a low risk of bias), and the Yang 2017[147] (fair quality) cohort study. There were no statistically significant differences between those receiving allograft and those receiving autograft in any of the studies. Three of these studies had data suitable for meta-analysis and have been added to the data meta-analysed for non-irradiated allografts in the Zeng 2015 review of reviews [102] referred to above. The inclusion of these three studies did not alter the overall non-significant mean difference seen in the Zeng meta-analysis (WMD, -0.45; 95% CI: -1.39, 0.48; P=0.34), see Figure 4. A random effects model was used as the statistical heterogeneity was moderate (I^2 56%) (Zeng 2015 used a fixed effect model). The Yang 2017 study was not a randomised comparison, removal of this study from the meta-analysis removed the heterogeneity and led to a statistically significant difference in favour of allografts (WMD, -0.93; 95% CI: -1.57, -0.28; P=0.005).

Table 13: Lysholm scores ACL studies

Lysholm Knee score at final follow-up, mean (SD) unless stated			
Yoo et al, 2017[144] ROB selection unclear	**Allograft, n=64**	**Autograft, n=68**	**P-value**
Endpoint value (Mean range)	93 (73-100)	96 (67-100)	ns
Tian et al, 2016[145] ROB selection unclear	**Allograft, n=59**	**Autograft, n=62**	
Baseline value Endpoint value	57 (8) 89 (11)	58 (10) 90 (10)	0.6015
Jia et al, 2015[136] ROB selection low	**Allograft, n=53**	**Autograft, n=53**	
Baseline value Endpoint value	71.0 (3.6) 86.8 (2.6)	71.9 (4.2) 85.2 (3.1)	 0.94
Yang et al, 2017[147] Fair quality	**Allograft, n=85**	**Autograft, n=90**	
Baseline value Endpoint value	53.2 (5.8) 90.9 (3.3)	53.9 (6.1) 91.8 (2.8)	 0.053

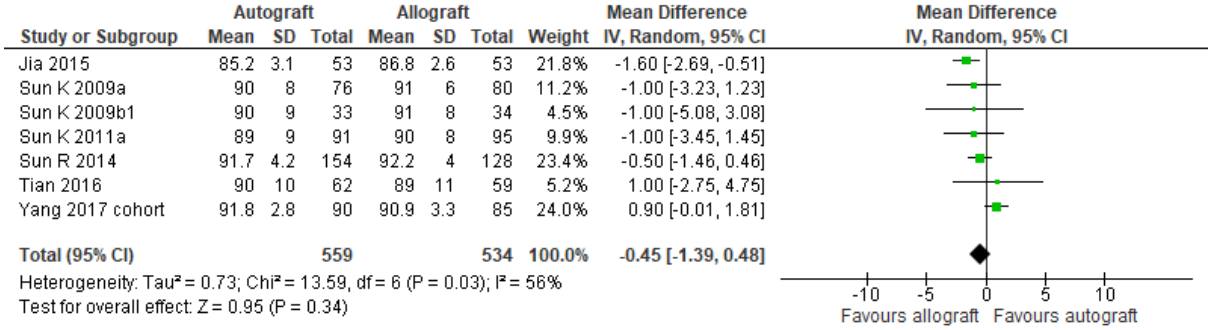

Figure 4: Updated meta-analysis of non-irradiated allografts versus autografts, Lysholm score

Three RCTs reported Tegner activity scores, see Table 14. There were no statistically significant differences between allograft and autograft in these three RCTs, which all had unclear risks of selection bias. One RCT reported the mean Cincinnati knee score (Tian 2016[145]) and one other reported the Single Assessment Numeric Evaluation (SANE) score (Bottoni 2015[113]). Both studies had an unclear risk of selection bias. No significant differences were seen between groups in either study on these respective outcomes. Two of these studies data were suitable to meta-analyse and have been added to the data meta-analysed for non-irradiated allografts in the Zeng 2015 review of reviews[102] referred to above. The inclusion of these two studies did not alter the overall non-significant mean difference seen in the Zeng meta-analysis (WMD, 0.14; 95% CI: -0.08, 0.36; P=0.22), see Figure 5. A fixed effects model was used as no statistical heterogeneity was identified (I^2 0%).

Table 14: Tegner activity scores, ACL studies

Tegner activity score at final follow-up, mean (SD) unless stated			
Yoo et al, 2017[144] ROB selection unclear	**Allograft, n=64**	**Autograft, n=68**	**P-value**
Change value (mean, range)	5 (3-8)	5 (2-9)	ns
Tian et al, 2016[145] ROB selection unclear	**Allograft, n=59**	**Autograft, n=62**	
Baseline value Endpoint value	2.9 (0.8) 7.8 (1.0)	2.8 (0.7) 7.9 (0.8)	 0.5438
Bottoni et al, 2015[113] ROB selection unclear	**Allografts, n=49**	**Autografts, n=48**	
Endpoint value	4.5 (2.2)	4.8 (2.3)	0.505

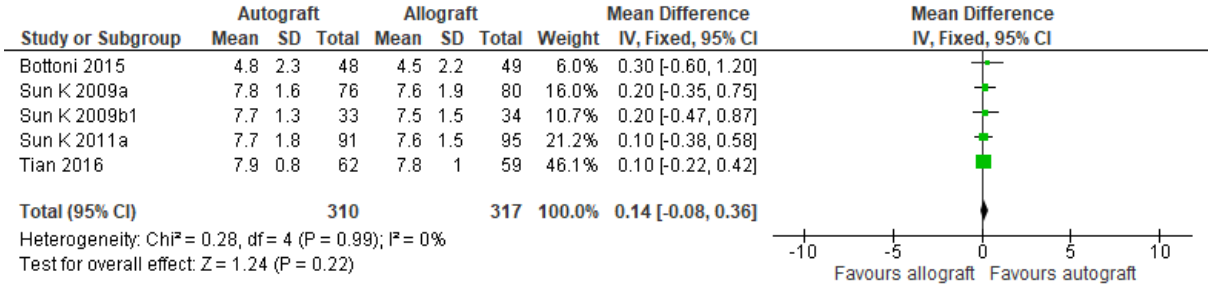

Figure 5: Updated meta-analysis of non-irradiated allografts versus autografts, Tegner score

Three RCTs reported the IKDC subjective score (see Table 15). The risks of selection bias were unclear in all but the Jia 2015[136] study which had a low risk of bias. There were no statistically significant differences between those receiving allograft and those receiving autograft in the four studies.

Table 15: IKDC subjective scores, AC studies

IKDC subjective score at final follow-up, mean (SD) unless stated			
Tian et al, 2016[145] ROB selection unclear	**Allograft, n=59**	**Autograft, n=62**	**P-value**
Endpoint value	89 (12)	90 (11)	0.633
Bottoni et al, 2015[113] ROB selection unclear	**Allografts, n=49**	**Autografts, n=48**	
Endpoint value	73.7 (25.9)	77.2 (25.4)	0.510
Jia et al, 2015[136] ROB selection low	**Allograft, n=53**	**Autograft, n=53**	
Baseline value Endpoint value	66.1 (3.5) 85.6 (2.9)	67.3 (2.5) 87.8 (1.6)	 0.90

Results – quality of life outcomes

None of the included studies reported quality of life outcomes.

Complications and adverse events.

Three studies reported complications or adverse events. In the RCT by Yoo 2017[144] the proportions of participants with major complications were 17.2% and 7.35% in the allograft and autograft groups respectively. The study reported that there was no statistically significant differences in these rates. Tian 2016[145] reported that there were no immediate postoperative complications requiring reoperation or readmission in either group in their RCT. In the Yang 2015[147] cohort study, rates of incision infection and joint swelling were higher in the allograft group, but the differences were not statistically significant**.**

Other prospective studies of allografts

Four RCTs (Tian 2017[139]; Dai 2016[140]; Niu 2016[141]; Kang 2015[142]) and one case series (Niu 2017[143]) also reported the effects of allograft for primary ACL reconstruction. These studies compared different ways of using allografts (see Table 11). 543 participants were enrolled in these studies (although the numbers actually analysed were lower) which were all conducted in China. The mean length of follow-up ranged from 31 to 68 months. The eligibility criteria or indications for allografts differed between the studies, see Table 12. Concurrent procedures were reported in three studies as described in Table 12; between 33-53% of participants had a concurrent procedure. The mean age of participants was between 24 and 30 years, with males making up between 47-80% of participants. In the light of the comparative studies described above and the results of the meta-analysis, these studies are only briefly discussed.

Tian and colleagues[139] from Qingdao University, Shandong, compared irradiated versus non-irradiated (fresh-frozen) double bundle hamstring allografts in a RCT with 83 patients.

The other four studies came from Hebei, China, three from Third Hospital, Hebei Medical University and one (Kang 2015)[142] from Shijiazhuang No 1 Hospital.

Niu and colleagues (2017)[143] in a non-randomised study, compared results in 47 patients who had a double BPTB allograft with 51 with a single layer BPTB allograft.

Niu and colleagues (2016)[141] compared double layer BPTB and four strand hamstring tendon allografts in an RCT with 101 patients.

In an RCT with 129 patients, Dai et al (2016)[140] compared six-strand hamstring and BPTB allografts.

Kang 2015[142] compared single-bundle BPTB, modified to give a larger graft, with double-bundle tibialis anterior allografts in an RCT with 94 patients. The rationale was that double bundle would provide replacement of both the functional bundles of the original ACL (antero-medial and postero-lateral).

Results – Functional outcomes

The IKDC subjective score was reported in all five studies (Tian 2016[139]; Niu 2016[141]; Niu 2017[143]; Dai 2016[140]; Kang 2015[142]). In three of these (Tian 2016[139]; Niu 2016[141]; Niu 2017[143]) no baseline values with which to compare before and after allograft were reported. In the RCT by Dai 2016[140], which had an unclear risk of selection bias, both six-strand hamstring allograft and BPTB allograft appeared to show improvements on the IKDC subjective score at 4 years follow up. The IKDC subjective score

in Kang 2015[142] also appeared to show improvements between baseline and follow-up in single bundle and double bundle allograft groups. This study also had an unclear risk of selection bias.

The Cincinnati score was a reported outcome in Tian 2016[139], however, there were no baseline values in which to compare before and after allograft.

The Lysholm score was reported in all five studies. In the RCTs by Tian 2016[139], Niu 2016[141] and the case series by Niu 2017[143] no baseline values for the lysholm score were reported. In the Dai 2016[140] RCT both six-strand hamstring allograft and BPTB allograft appeared to improve at 4 years follow up. In Kang 2015[142] both single bundle and double bundle allografts also appeared to improve the Lysholm score at follow up. Kang et al[142] concluded that the modified single bundle BPTB graft gave as good stability (both antero-posterior and rotational) as the double bundle anterior tibialis graft, and recommended the BPTB for ACL reconstruction.

Two studies reported the Tegner score. One (Tian 2016[139]) did not report baseline values. The other, Kang 2015[142], appeared to show improved Tegner scores for both single bundle and double bundle allografts.

Tian and colleagues (2017)[139] found anterior and rotational laxity to be much more common with irradiated allografts (side to side differences with KT-2000 of over 3mm in 14% after non-irradiated grafts and 64% with irradiated ones).

Tian et al 2017 concluded that hamstring allografts irradiated with 2.5 Mrad should not be used.

Dai et al 2016[140] concluded that the six-strand hamstring allograft (semitendinosus and/or gracilis, folded into a multi-strand graft) gave better stability than single-bundle BPTB allograft.

Results – quality of life outcomes

None of the included studies reported quality of life outcomes.

Results – Failure and revisions

ACL re-rupture and revision rates were 6.2% in six-strand hamstring allograft and 10.3% in the BPTB allograft groups in the RCT by Dai 2016.[140] Re-rupture of grafts after high-energy traumas were 2% in the DBPTB allograft group and 7.8% in 4SHS allograft group, and graft failure rates 4% and 17.6% for the two groups respectively in the Niu 2016 RCT.[141] In the Niu 2017[143] case series, the rates of re-rupture of the reconstructed ACL were 2% in the DBPTB allograft and 12% in BPTB allograft groups.

Niu et al[143] reported better results (success rates, anterior stability and knee function) with the double BPTB allograft compared to the single one.

Results – progression of osteoarthritis

Tian 2017[139] reported progression of osteoarthritis, measured using KL grading compared with the non-operated knees, in 11.4% in the non-irradiated allograft group and 30.8% in the irradiated allograft groups.

Adverse events

Tian 2016[139] reported no major complications. The remaining studies stated that there were no complications.

Hardy and colleagues[149] provide a systematic review specifically on the adverse events after harvesting autografts for ACL reconstruction. They note that in France most ACL reconstructions are done with autografts, taken from hamstring tendons, patellar tendon and fascia lata. They included 36 articles in a good quality review. For hamstring autografts, they conclude that there are complications in 8.3% of cases (though some studies have much higher rates). The commonest is saphenous nerve damage, though they think this is largely avoidable by a different approach. Temporary strength deficits (up to 3 months) occur. Because these complications are temporary, they will have insignificant impact on the long-term economics.

They estimate fewer complications with PT (0.2% to 1.2% overall) but some more serious, including patellar fracture in 0.42% to 1.3%, rupture of PT and anterior knee pain, reported in as many as 46%, but with varying definitions.

Revision ACLs

No prospective studies in revision ACL were identified.

A small retrospective study by Saper and colleagues[150] highlights what may be a growing problem – more ACL ruptures and second ruptures in adolescent athletes taking part in contact and "collision" sports, at higher level. In their series of 21 athletes, the average age of surgery was 16.5 years, and mean time to revision ACLR being required was 13 months. Almost half of the athletes were female. Good results were obtained after revision ACLR with 68% returning to pre-injury levels. Although over half of the whole group were involved in collision sports, most second tears did not involve contact. The commonest sport was American football, followed by basketball and soccer. One wonders how long before they return with further ruptures.

We included six studies that were retrospective analyses of prospective data, see Table 16. Three of these were primary PCL reconstructions and two were revision PCLs and one included both. Participant characteristics, sample sizes and outcomes assessed differed between the studies.

Other retrospective studies are summarised in Appendix 3.

Table 16: Included studies retrospectively analysing prospectively collected data in ACL

Reference and study details	Participant characteristics	Key results (from abstracts)
Cinque et al[151] Retrospective analysis of prospectively collected data (database)	Aged between 20 - 30 years or 50 - 75 years. Primary ACL Sample size: 85 (younger 52, older 33) Follow-up: younger 3.4 years, older 3.1 years	Significant improvement in outcome scores from pre- to postoperative assessments found in both groups. The younger cohort had significantly lower postoperative WOMAC scores (P = 0.025). No significant differences were found between the younger and older cohorts in postoperative SF-12 PCS (P=0.487), SF-12 MCS (P=0.900), Lysholm score (P=0.660), IKDC score (P=0.256), Tegner activity score (P=0.420). No re-tears occurred in either group, and rates of arthrofibrosis surgery were comparable (12% older cohort vs 13% younger cohort).
Nelson et al (2016)[152] Retrospective analysis of prospectively collected data (registry)	Skeletally immature (< 17.0 years old) with an open physis Primary ACL Sample size: allograft 91, autograft 443 Follow-up: 2.9 years	The incidence rate for revision for allografts was 13.2 % and autograft 7.5%, no significant difference after adjusting for confounders
Steadman et al (2015)[153] Retrospective analysis of prospectively collected data (registry)	Aged 18 to 70 years, primary BPTB ACL autograft or allograft reconstruction Primary ACL Sample size: 192 (allograft 96; autograft 96) Follow-up: allografts 4.7 years (range, 2.0 to 9.8); autografts 8.6 years (range, 2.0 to 16.2)	The revision rate for allograft group was 14%, no autografts required ACL revision. There was no significant difference between allografts and autografts for mean Lysholm (85.6 v 83.4; P =0.43), or mean Tegner (6.0 v 5.4; P=0.09)
Fox et al (2004)[121] Retrospective analysis of prospectively collected data (database)	All patients who underwent a revision ACL reconstruction with nonirradiated patellar tendon allograft Revision ACL Sample size: 32 (of 38) Follow-up: 4.8 years (range 2.1 to 12.1 years; SD 29.3)	Postoperative mean results: Noyes sports function (72), Lysholm (75), Tegner (6.3), KOOS sports activity scale (67), SF-12 physical component (48), SF-12 mental component (55), and IKDC (71). The Noyes sports activity score showed a significant improvement from 55 preoperatively to 70 at follow-up. One patient required another revision

Smith et al (2005)[154] Retrospective analysis of prospectively collected data (database)	All patients who had a revision ACL reconstruction with non-irradiated patellar tendon allograft, minimum 2-year follow-up. Sample size: 32 Follow-up: 4.8 (range 2.1 – 12.1) years	28% reconstructions failed using clinical criteria (defined as either the presence of a pivot shift, and/or greater than 5 mm side-to-side difference on KT-1000 testing). There were no postoperative infections. No additional surgeries were performed. There was no clinical evidence of graft rejection.
Zaffagnini et al (2017)[155] Retrospective analysis of prospectively collected data (database)	Primary or multiple ACL revision with double-bundle technique using Achilles tendon allograft; sport practice at regular bases with a minimum Tegner Activity Level of 7 before the indexed knee injury; no lower limb malalignment or malalignment corrected within 6 months from the indexed surgery Sample size: 26 Follow-up: 6.0 (SD 1.6) years)	69% returned to sport both at elite (44%) or county level (56%) after a mean 6.7 (SD 1.5, range 3–9) months. Mean Lysholm score improved from 64.4 (SD 8.1) pre-operative to 83.8 (SD 11.3) at final follow-up (P<0.0001). 30% of patient scores were rated as excellent, 39% as good, 22% as fair and 9% as poor. 12% experienced a further graft rupture after a mean 2.6 years, (range 3.5–48 months). Overall survival rate at mean six years follow-up was 81%.

Irradiation

The high quality review by Zeng[102] showed no difference in success rates when allografts were compared with non-irradiated grafts, but that autografts were more successful than irradiated grafts. An earlier good quality systematic review by Lamblin et al 2013[156] looked specifically at ACL reconstruction with autografts versus non-irradiated, non-chemically processed allografts and found no difference in clinical function outcomes or failure rates.

Another recent good quality review by Grassi et al[103] compared allografts and autografts in revision ACL reconstruction. Overall, autografts were better, but once studies using irradiated allografts were excluded, there were no differences in outcomes.

Wang et al 2018 [157] reviewed studies (four RCTs and two cohorts) that compared irradiated allografts with autografts, and found that autografts gave better results for some outcomes such as knee stability and patient satisfaction, but no difference with other measures. Failure rates in the cohort studies were 4% with allografts and 2% with autografts. No failures were reported in three of the RCTs.

The purpose of irradiation is to reduce the risk of infection, which could be bacterial or viral. However the high doses required to eliminate viruses (up to 5.0 Mrad to eliminate viruses such as HIV) reduce the biomechanical strength of the allograft (Park 2014[112]). Other methods of processing allografts, such as freezing, reduce but may not completely eliminate transmission.

So the dose of radiation may be important. Studies have used a range of doses of gamma irradiation. Doses between 1.0 and 2.5 Mrad are sometimes referred to as "low dose" (Park et al[112]. Li et al 2016[158], Sun et al 2015[159], and Tian 2016[148] used 2.5 Mrads. Lenehan et al 2015[160] and Engelman 2014[161] used<2Mrads. Rose et al 2016[162] and Cooper et al 2004[163] used <1.8Mrads (but some were non-irradiated). Tejwani et al 2015[164] had two subgroups, >1.8 Mrad and ≤ 1.8 Mrad. The higher radiation group had a higher failure rate. They also found that the use of BioCleanse was associated with a higher failure rate.

Curran and colleagues[165] carried out a laboratory study comparing low-dose irradiated and non-irradiated BPTB allografts and found that irradiation reduced allograft strength

Park et al 2014[112] reviewed the effect of irradiation, using 21 studies published up to September 2012, with 415 irradiated and 1038 non-irradiated allografts. They noted that the use of allografts had increased considerably. They excluded studies that use high-dose irradiation (defined as > 2.5 Mrads). Of the 21 studies found, four reported on irradiated allograft only, 15 on non-irradiated allografts, one, Guo 2012[166], reported a non-randomised comparison of both, and only one, Sun et al 2009[116], was an RCT comparing irradiated and non-irradiated BPTB allografts. No details are given of any quality assessment of the primary studies. Park and colleagues provided several meta-analyses and concluded that irradiated grafts in primary ACL reconstruction results in poorer Lysholm scores (84 versus 90, p <0.05), poorer stability (with Lachman, pivot-shift and KT-1000/2000 all statistically significantly poorer, though with considerable heterogeneity in effect size) and more revision surgery, though revision rates were low (2.5% in irradiated and 0.2% with non-irradiated). However rupture rate was slightly lower with irradiated grafts (but p = 0.5). Just over half the grafts were BPTB.

Given the heterogeneities involved – type of graft, methods of preservation – and that most of the included studies were case series of one method only, Park et al express caution in interpretation.

The two studies in the Park 2014 review that compared irradiated and non-irradiated grafts were Sun 2009[116] and Guo 2012.[166]

Sun 2009 was from the Qingdao University group in Shandong, China, and though small, has the strongest design. They randomised 99 patients to BPTB autografts, irradiated allografts and non-irradiated allografts. Details of randomisation and allocation concealment are very brief ("using a computer"). Assessment of outcomes was done by an orthopaedic surgeon who was unaware of the type of graft used, though the patients were aware. One surgeon did all the reconstructions. In brief, Sun et al found little difference between autograft and non-irradiated allografts, but poorer results with irradiated (2.5Mrad). They report failures rates of 34% with irradiated and 8.8% with non-irradiated allografts, and 6.1% with autografts, where failure was defined as a side to side laxity difference (KT-2000) of > 5 mm. There was one case of late infection in a non-irradiated allograft recipient, which resolved with antibiotic treatment without any surgical procedure being required. The results led the group to end the use of irradiated grafts.

The more recent RCT from the Shandong group, by Tian et al 2017[139], has been summarised above. It reported greater laxity with irradiated hamstring tendon grafts.

Guo et al 2012[166] from Chongqing, China, compared results in 41 patients who had autografts, 33 who had fresh-frozen allografts, and 68 who had gamma-irradiated allografts. The irradiated grafts were also frozen at minus 35 degrees C for at least three months. After mean follow-up of almost 7

years, there was greater laxity (KT-1000) and a higher failure rate (8.8%) after irradiated grafts. The proportions with KT-1000 > 5mm were 3% with non-irradiated allografts (95% CI 0-6%) and 18% for irradiated grafts (9-27%). Guo et al note the non-randomised nature of their comparison and the relatively small numbers, and hence the lack of power, and recommend a larger study. But they advise against the use of irradiated graft for ACLR.

A more recent, very large observational study by Maletis and colleagues from Kaiser Permanente [167] gives results from 5586 patients who had ACL reconstruction with BPTB grafts, 82% with autografts and 18% (rounded) with allografts. The 18% represents 1029 patients, whose allografts were treated with different combinations of radiation, and chemical processing. The main outcome measure was the need for revision at 2 years, when allografts had an overall rate of 4.1% and autografts a rate of 1.7%. At that time point, there was little difference amongst the allograft groups, and the abstract of the study reports that irradiation made little difference. However their KM curve to 6 years shows that the revision rates in the low radiation allograft groups and the autograft group, were 6% and 4% respectively. The higher radiation groups (> 1.8Mrad) had revision rates of about 10%. However the data come from the years 2005 to 2012, and most patients had irradiated or chemically processed allografts.

Another observational study from the Kaiser Permanente ACLR register group by Maletis et al 2017 [167] examined both choice of graft (BPTB autograft, hamstring autografts, and "soft tissue" allografts from hamstring, tibialis anterior and posterior, and peroneus) and method of processing (radiation and chemical, both, or none) in 14,015 cases. The chemical processing methods included Allowash and AlloTrue, with added irradiation, and BioCleanse without irradiation. The unprocessed allografts were fresh-frozen. Radiation could be < or > 1.8 Mrad, both with or without chemical processing. The primary outcome was aseptic revision. The rates of this were quite low, with crude cumulative revision rates by 3 years of 2.5% (95% CI 2.0-3.1%) for BPTB autografts, 3.5% (95% CI2.9-4.2%) for hamstring autografts, and 3.7% (95% CI 2.9-4.7%) for allografts. In brief, allografts irradiated with 1.8 or more Mrads had higher failure rates than autografts, as did allografts processed with BioCleanse alone. There was no difference in revision rates between hamstring autografts and allografts irradiated with <1.8 Mrads, nor between unprocessed allografts and autografts. But there was a difference between BPTB autografts and hamstring autografts, with the latter having a 50% higher revision rates after adjustment for age, sex and race. (The mean age of those receiving allografts was about 10 years older than the autograft group, which implies that there may have been other differences not captured by the registry.) Unfortunately follow-up was only up to 2 years.

Infections after allograft reconstruction might be grouped as;

- Superficial wound infections
- Deep infections, resulting in septic arthritis of the knee, which are rare (about 0.5%)
- Disease transmission due to non-sterility of the allograft, with the main concerns being viral infections such as hepatitis and HIV.

The main aim of sterilisation, by irradiation or other means, is to prevent infections. However, as Park et al point out, doses of 2.5 Mrad will not inactivate the viruses. Doses high enough to kill the viruses (say 3-5 Mrad) weaken the grafts. So "low-dose" irradiation may not be doing much good for virus eradication, but also appears to weaken the graft.

However, the risk of infection with bloodborne viruses such as HIV and hepatitis viruses is extremely low. In 2008, Mroz and colleagues[168] reviewed all musculoskeletal (including bone and soft tissues)

allograft-tissue recall data from 1994 to 2007. Recipient infections accounted for only 10% of recalls, but all were bacterial, especially Clostridium. Mroz and colleagues note that only two cases of HIV transmission by allografts have been reported, in 1985 and 1988 (bone for spinal fusion). There have been reports of one case of hepatitis B and two of hepatitis C transmission, but the most recent was in 2002.

The FDA published guidelines for nucleic acid testing for HIV and HCV in 2005, updated in 2010 and 2017[169]. Screening of allograft donors has been greatly improved in the USA. So there at least, the need for sterilisation by radiation or chemical cleansing may now unnecessary. The EU has also required tissue banks to have biovigilance programmes.

Project NOTIFY is a WHO-led surveillance project of adverse outcomes of allograft use. Hinsenkamp and colleagues[170] provide details of viral transmission from allografts. There were nine reported HIV infections, the most recent being in 1996, 10 cases of HCV infection, the most recent being in 2000. No cases of HCV transmission have been reported since nucleic acid testing (NAT) was introduced. NAT testing reduces the period in which donors could be infectious but antibody negative.

A systematic review by Dashe et al[171] considered the effects of different levels of irradiation and concluded that the optimum dose taking account of sterility and graft strength was 2.2 Mrad. However no data on sterility was provided, and it is not clear how the threshold dose of 2.2 Mrad was chosen. Of the six studies they included, five used 2.5 Mrad, and even the one that used 2.0 to 2.5 Mrad reported more failures in the irradiated group (33% versus 2.4% in the non-irradiated group, even with a large (27%) loss to follow-up.

There is less evidence on low dose (defined as 1.0 to 1.2 Mrad) but Yanke and colleagues reported a small laboratory study with 10 BPTB grafts irradiated and 10 not. The only significant different was a reduction in graft stiffness in the irradiated group, and Yanke et al concluded that low dose irradiation was not harmful. However if it was too low to ensure sterility, there seems little point. A later review from the same group [172] examined laboratory results in cadaveric and animal studies, and found variable results with low dose irradiation, but consistently deleterious results with high dose irradiation.

Yu et al[173] from Kaiser Permanente used their registry data to examine infection rates amongst 10,190 allograft cases, of which 83% received a processed allograft (chemical and/or irradiated) and 17% received an unprocessed allograft. The incidence of deep infections was 0.15% and was no different – processed versus unprocessed OR 1.36, 95% CI 0.31-6.04.

In summary;

- Sterilisation of allografts is much less necessary than in past decades, because of serological testing of donors and medical record review
- Tissue banks use combinations of physical, chemical and radiation methods to reduce the risk of infection
- Doses of radiation >1.8 Mrad are insufficient to kill viruses, but they are sufficient to damage allografts
- This raises the question as to whether radiation at these levels should be continued
- Lower levels of irradiation may be less damaging to graft structure and are aimed at eliminating bacteria.

- So has the time come to end high-dose irradiation of allografts?

Could the negativity perceptions amongst some surgeons about failure of allografts have come from the historical high use of irradiation and subsequent series of high failures?

Discussion

We note an evidence review from New Zealand from ACC Research[174], produced to guide practice. It was based on an overview of 12 systematic reviews. The primary studies were not examined. The last search was done in May 2016, and the reviews were published from 2007 to 2015. The ACC report concluded that there was no evidence of any significant differences in failure rates or other outcomes, between autografts and non-irradiated allografts. It concluded that allografts irradiated with low doses still performed less well than non-irradiated allografts, and that low doses were not sufficient to eliminate the risk of disease transmission. Given the similar outcomes, cost became the determining factor. It appears that costs of allografts are higher in NZ than elsewhere because there is no local provider.

Older studies may not reflect modern processing methods. Fresh frozen allografts give better results. Mardani-Kivi et al[175] found no difference in outcomes between fresh-frozen tibialis posterior allografts and hamstring autografts after 55 months. Krych et al [176] reported a meta-analysis showing that BPTB autografts did better than allografts, but the advantage only applied when allografts were irradiated or chemically processed.

Cost-effectiveness of anterior cruciate ligament (ACL) reconstruction

Our analysis starts from the decision to reconstruct. Non-operative approaches have been tried but do not give good results, and are not cost-effective (Saltzmann [177]) whereas ACL reconstruction gives good results, and allows people to get back to vigorous, and indeed international level, sport. A cost-effectiveness analysis by Stewart and colleagues [91] concluded that ACL reconstruction was cost-effective compared to physiotherapy and no reconstruction in competitive athletes,

The outcomes after ACL are;

- Permanent success
- Temporary success, possibly due to a new injury after return to activities. A revision ACLR can be done, and may be more likely to use allografts given prior autografts. But autografts could still be used (contralateral hamstrings or BPTB)
- Graft failure, in about 6%
- Donor site morbidity with symptoms such as knee pain (particularly anterior after BPTB autografts), instability and knee extension loss. The latter might be an indication for a revision operation if problematic.
- Infection, which appears to be rare.

Instability is measured Lachman's test for anterior laxity and the pivot-sift test for rotational laxity.

Salzmann and colleague[177] provide a review of 24 economic studies in ACLR. They note that 17 were reports only of costs, of which five compared autograft and allograft ACLR. The other 7 include three cost-utility studies of ACLR versus non-operative management, with all three concluding that surgery was more cost-effective. Two studies compared the cost-effectiveness of single versus double-bundle techniques. One study compared prompt versus delayed ACLR. The remaining study by

Genuario 2012[178] was the one most relevant to this review, because it compared autografts with allografts.

Some studies report small differences in in-patient stays. Gorschewski et al[115] reported mean stays of 5.2 days for allografts and 6.3 days for autografts. They also reported a slightly earlier return to work after allografts (2.3 months versus 2.6 months, p = 0.004).

Cooper and Kaeding [179] report hospital costs for ACL reconstruction of $4,072 for autografts and $5,195 for allografts. The slightly shorter theatre time for allografts had little effect on the cost differential.

Barrera Oro et al 2010[180] also report that operating time was 12 minutes longer with autograft but the total cost was about $1000 more with allograft.

Cohen et al 2017[181] report that saphenous nerve damage is commoner after ACLR with autografts, but not enough to be economically significant.

Gries et al 2012[182] compare costs of tibialis allografts with hamstring autografts in Utah. The mean cost of ACLR allografting was $4,587 with theatre time 92 minutes. The autograft cost was $3,489 with 125 minutes of theatre time.

Cole et al[183] from North Carolina report hospital charges of $4,622 for allografts and $5,694 for autografts. The difference is due to longer operating theatre time and longer inpatient stays for autograft patients.

Archibald-Seiffer et al from Salt Lake City[184] report very large variations in costs of ACL reconstruction.

One issue to be considered in interpretation of all cost-effectiveness studies is how old the clinical effectiveness data that supports them is. For example, older studies may have a mixture of allografts sterilised by different methods, including radiation. The high quality review by Zeng[102] showed no difference in success rates when allografts were compared with non-irradiated grafts, but that autografts were more successful than irradiated grafts.

Deep infection around graft is uncommon but costly – surgical washout (arthroscopic) then 2 weeks IP stay for IV antibiotics (teicoplanin) then 6 weeks oral flucloxacillin and rifampicin.

In the UK, present practice is to start with autografts. However in the modelling we include allografts as a first line option. We then assume that if first graft is an allograft, so would any subsequent grafts.

For modelling purposes, there are two main arms to consider, and a possible third. The main ones are;

- ACLR with autograft
- ACLR with allograft

A third option has occasionally been reported, a hybrid of autograft reinforced with allograft, but this approach is not discussed further in this report.

Autografts can be hamstring or BPTB, but there does not seem to be a lot to choose between them when used as first repair.[135]

For hamstring autografts, the tendons of the two smallest muscles, the gracilis and the semitendinosus, are used. The whole tendons are removed from within their sheath but sufficient power remains in the larger hamstring muscles for this not to cause problems in most sports-people. There are a few reports of some reduction in maximum speed.[94] The tendons may partially re-grow.

The combination of the doubled gracilis and semitendinosus tendons is stronger than the BPTB autograft.[95] Conversely, BPTB autografts are believed to be quicker to incorporate, as they have bone-to-bone healing.

BPTB grafts may be used in second reconstructions if the tunnels are too wide for hamstring grafts. An alternative would be to have a two-stage procedure with bone grafting to the tunnels first, then ACL reconstruction.

The modelling assumes there is a no clinical reason to prefer one type of graft over the other. In the clinical scenario, especially in revision ACLR, there are settings where one graft type may not be technically feasible (for example, fixation cannot be achieved due to bone loss). So there are scenarios where an allograft might be considered essential, regardless of the difference in cost. These scenarios have not been included in the modelling because choice is not an option. They may need to be considered when preparing a guideline or recommendation.

Analysis

The aim of this analysis is to determine whether an autograft or an allograft is the more cost-effective option in anterior cruciate ligament (ACL) reconstruction.

Patients having an ACL reconstruction, will have a number of outcomes:

- Permanent success – where symptoms are relieved;
- Failure – followed by another reconstruction;
- Failure - but a patient may decide against another reconstruction and opt for conservative care including physiotherapy.

Model structure

A decision tree model in Microsoft Excel® was considered the most appropriate choice as ACL reconstruction is usually successful and most patients return to a functioning knee after reconstructive surgery. The starting point for the economic model is the decision to do an ACL reconstruction (we have not included a non-reconstruction arm in the model). The clinical pathways were developed using information from the published literature and clinical experience. Figure 6 shows the different clinical pathways.

The pathway assumes that a patient needing ACL reconstruction either has an allograft or a hamstring (HS) autograft as a first reconstruction. After the first ACL reconstruction, there are two outcomes:

1. Success with symptoms resolved and full function restored
2. Failure of the reconstruction with continuing symptoms.

Allograft pathway

For simplicity, we have assumed that surgeons who start with an allograft, will use allografts in any further reconstructions. This may not be entirely correct, in that if a first allograft failed, some

surgeons might opt for autograft in the second procedure, if they thought autografts less likely to rupture.
If the first allograft reconstruction fails, patients can either have another reconstruction (second allograft) or conservative care. The latter consists of an orthopaedic consultation visit post-operation and eight physiotherapy sessions.

The second allograft reconstruction can succeed or fail. If the second allograft reconstruction fails, patients can either have a third allograft reconstruction or conservative care as outlined before.

A third and final allograft reconstruction can either be a success or a failure. For those that have failed the third allograft reconstruction, we have assumed that the only option is conservative care.

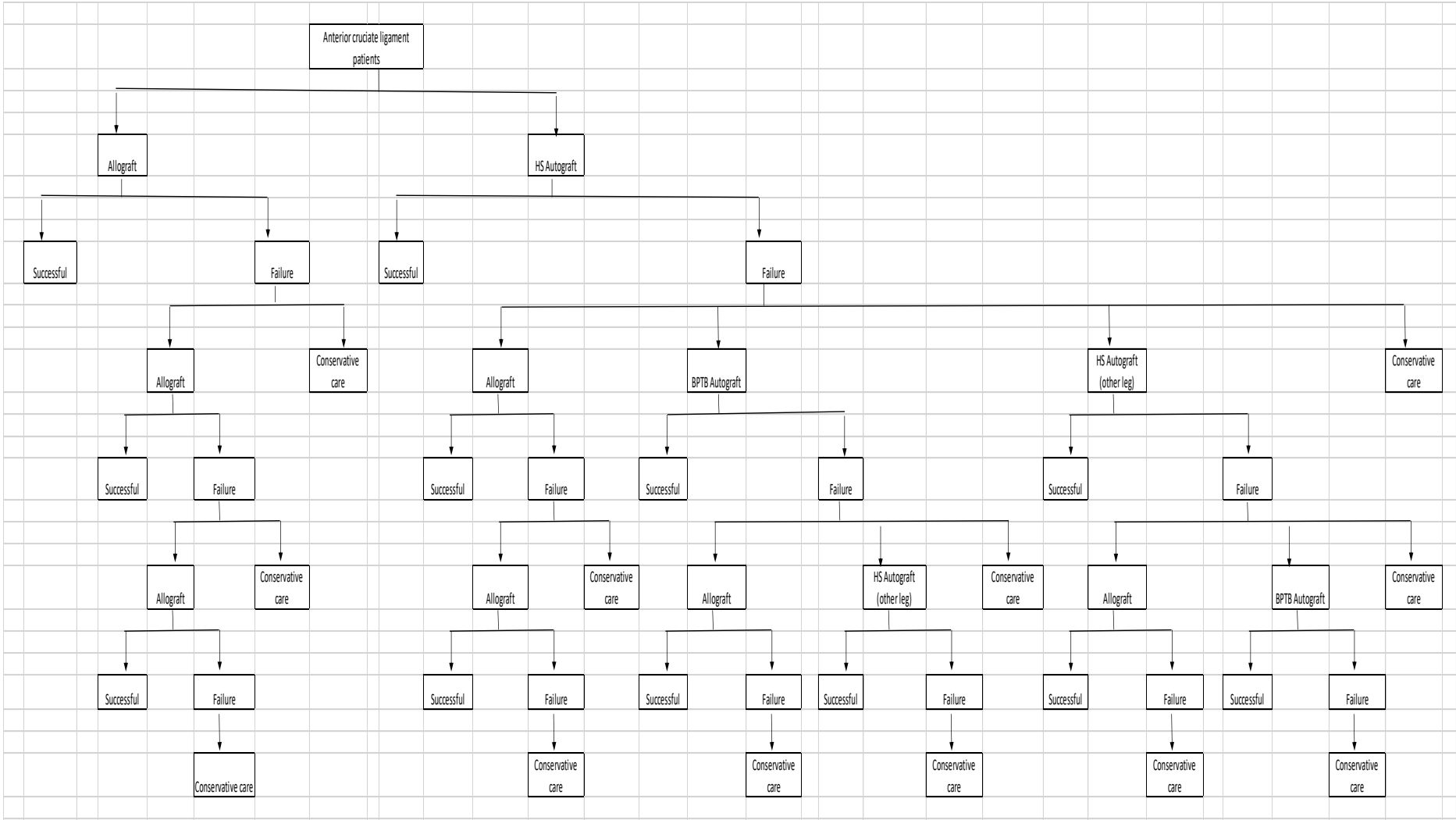

Figure 6: ACL clinical pathway

Hamstring autograft pathway

We have assumed that in first reconstruction the autograft is from the hamstring muscles on the same leg as the ACL rupture. If the first HS autograft reconstruction fails there are four choices:

1. An allograft
2. BPTB autograft
3. HS autograft (from other leg)
4. Conservative care.

The BPTB option (whether allograft or autograft) may be useful in the revision setting if the tunnels are too wide. If the second reconstruction used contralateral HS autografts, a two-stage procedure might be necessary, with bone grafting of tunnels before ACL reconstruction.

The allograft option (option 1) can either be a success or a failure. Failures can have another allograft or conservative care.

BPTB autograft reconstruction (option 2) can either be a success or a failure. Failure can be followed by an allograft, an HS autograft (from other leg) or conservative care.
An HS autograft from the other leg (option3) can succeed or fail. After failure, the options are an allograft, BPTB autograft or conservative care.

In all scenarios, if the third reconstruction fails the only option is conservative care.

A simplified version of the pathways is shown in Table 17.

Table 17: Different combinations for ACL reconstruction

1st line	**2nd line**	**3rd line**
Allograft	Allograft	Allograft
Hamstring autograft	BPTB autograft	Hamstring autograft (other leg)
		Allograft
	Hamstring autograft (other leg)	BPTB autograft
		Allograft
	Allograft	Allograft

Base-case analysis

For the base-case analysis, we adopted a three-year time horizon. We have not differentiated by gender or taken mortality into account. The starting age for a patient is 25 years. The analysis is conducted from the perspective of the UK National Health Service (NHS) and personal social services (PSS). All costs are in pounds sterling (£) in 2016/2017 prices. Health outcomes are measured in quality-adjusted life years (QALYs). Results are expressed as incremental cost-effectiveness ratio (ICER) more commonly known as a cost per QALY gained. An annual discount rate of 3.5% is applied to both costs and outcomes in line with recommended guidelines.[185]

Model inputs

Probabilities

For the base-case analysis, probabilities for the decision model were obtained from the literature and clinical expert opinion (see Table 18). For the 1st ACL reconstruction these probabilities were

obtained from a systematic review and meta-analysis of randomised controlled trials which focused on autograft versus allograft in ACL reconstruction by Zeng et al 2016[102]. Five trials were included in the forest plot meta-analysis for the subgroup analysis of autograft versus non-irradiated allograft failure (Lawhorn 2012[186]; Noh 2011[187]; Sun 2009[116]; Sun[117]; Sun K, 2011a[188]). There were 16 events in the autograft arm which resulted in a failure rate of 5.57% (n=287) and there were 20 events in the allograft arm with a failure rate of 6.92% (n=289).

Table 18: Key probabilities for ACL reconstruction

Pathway	Probability	Source
Allograft pathway		
1st Allograft		
Success	0.9308	
Fail	0.0692	Zeng et al [102]
2nd or 3rd Allograft		
Success	0.9643	
Fail	0.0357	Mohan et al 2017 [104]
HS autograft pathway		
1st HS Autograft		
Success	0.9443	
Fail	0.0557	Zeng et al
2nd or 3rd Allograft		
Success	0.9643	
Fail	0.0357	Mohan et al (2017)
2nd or 3rd BPTB Autograft		
Success	0.9590	
Fail	0.0410	Mohan et al (2017)
2nd or 3rd HS Autograft (other leg)		
Success	0.9590	
Fail	0.0410	Mohan et al (2017)

For the second ACL reconstruction, probabilities were obtained from the paper by Mohan and colleagues[104], who conducted a random effects meta-analysis of clinical outcomes in revision ACL reconstruction. The primary outcome was graft failure. Eight studies with a combined number of 2,302 patients provided an autograft failure rate of 4.1% (95% CI: 2.0-6.9%) and two studies with a combined number of 671 patients provided an allograft failure rate of 3.57% (95% CI: 1.38-6.74%).

For patients in whom the allograft failed, we have assumed based on expert opinion that 95% of them would have another allograft and 5% would have conservative care.

For patients in the HS autograft pathway, if it fails we have assumed based on expert opinion that 50% would have a BPTB autograft, 22.5% would have an allograft, 22.5% would have a HS autograft (from other leg) and the remaining 5% would have conservative care. In patients in whom the second HS autograft (from the other leg) fails, 71.25% would have an allograft, 23.75% would have a BPTB autograft and the remaining 5% would have conservative care. If the second BPTB autograft fails, 71.25% would have an allograft, 23.75% would have a HS autograft (from other leg), and the remaining 5% would have conservative care. If the second allograft fails, we have assumed that 95% would have another allograft and 5% would have conservative care.

Utilities

For patients who have a successful ACL reconstruction, we have used the population norm values provided by Ara and Brazier[82] which take into account a natural decline in quality of life associated with age. The utility value for a 25-year old in normal health is 0.9342 (see Table 19).

Genuario and colleagues[178] reported utility values for different types of graft for ACL reconstruction. These utility values were based on patients who attended a sports medicine clinic and completed a time-trade off exercise. This involved patients valuing different health (outcomes) states, and how much life they would be willing to give up being in a well state (assigned a value of 1, full health) to avoid a poorer outcome. For patients in whom either an autograft or an allograft fails, we have assigned a utility value of 0.790, which corresponded to the instability health state. Based on expert opinion the same utility value (0.7900) was also assigned to conservative care arm. For the few patients who get an infection, we have applied a disutility value for six weeks. These utility values were then weighted by the length of time in that health state to estimate quality-adjusted life years (QALY).

Table 19: Utilities for ACL reconstruction

Variable	Utility value	Source
Success	0.9342	Ara and Brazier (2010)
Fail	0.7900	Genuario et al (2012)
Conservative care	0.7900	Genuario et al (2012)

Resource use and costs

All unit costs reported in Table 20 are presented in pounds sterling (£) in 2016/17 prices. The cost of the allograft (£2,250) was obtained from the NHS Tissue Services price list for 2018/19 and was based on an average price of frozen whole semitendinosus medium (20-24cm) (TP6004) and frozen whole tibialis anterior medium (30-33cm).[189] We have not accounted for the price difference between the two financial years. There is no cost for the graft in the HS autograft arm. We have also added in the cost of the procedure, three consultant led follow-up clinics, eight physiotherapy sessions and the cost of analgesics (paracetamol and ibuprofen). We have assumed that a second or third ACL revision would cost the same as a first reconstruction (see Table 20).

We have also assumed that 0.3% of all reconstructions will get infections based on a recent ACL study by Waterman and colleagues.[190] The cost of infections was obtained from the Genuario et al paper[178] in US $ in presumably 2010 prices. We converted these costs into UK £ in 2017 prices using the World Bank gross domestic product (GDP) deflators[191] and the purchasing power parity (PPP) measures.[192] The cost of treatment for an infection included the cost of debridement, irrigation, and antibiotics started intravenously with one-week hospital admission then continued for a further 5 weeks.[193]

Conservative care costs were based on a follow-up consultant led outpatient clinic and eight physiotherapy sessions. Any costs not in 2016/2017 prices have been uplifted using the Hospital and Community Health Services (HCHS) index.[87]

Table 20: Resource use and costs for ACL reconstruction

Resource use	Unit cost (£)	Source
Graft type		
Allograft	£2,250	Tissue bank[189]
Procedure		
Intermediate knee procedures for non-trauma, 19 years and over (HRG code: HN24C)	£1,642	NHS reference costs 2015-16[86]
Other related costs		
Three non-admitted consultant led outpatient follow-up attendance (HRG code: WF01A)	£336	NHS reference costs 2015-16[86]
8 hospital physiotherapy sessions (30 mins)	£132	UCHSC 2017[87]
Paracetamol (two tablets twice a day per year)	£23.21	BNF 2016-17[88]
Ibuprofen (one tablet a day per year)	£12.47	BNF 2016-17[88]
Total costs		
Allograft	£4,395	
HS autograft	£2,145	
BPTB autograft	£2,145	
Infection		
Infections	£7,761	Genuario et al (2012)[178]
Conservative care		
One consultant led outpatient follow-up attendance (HRG code: WF01A)	£112	NHS reference costs 2015-16[86]
8 hospital physiotherapy sessions (30 mins)	£132	UCHSC 2016[194]

Results

Table 21: Base-case deterministic discounted results, ACL reconstruction

Procedure	Total mean costs £	Total mean QALYs	Incremental costs	Incremental QALYs	ICER*
HS autograft	£2,420	2.6980	-	-	-
Allograft	£4,846	2.6953	£2,426	-0.0026	Dominated

* ICER = incremental cost-effectiveness ratio

Table 21 shows the base-case deterministic results. Having an allograft as a primary ACL reconstruction is more costly (£2,426 more) and no more effective (very slightly less effective at 0.0026 QALYs - though this is not clinically significant) than having a HS autograft as a primary ACL reconstruction: that is, HS autografts dominated allografts. The main cost driver for this result was the cost of the graft. The second but less important factor was that the failure rate for allograft was slightly higher, by 1.3% (6.9% versus 5.6%) than the HS autograft. However this has little impact compared to allograft cost.

Sensitivity analyses

1) Secondary analysis comparing BPTB autograft vs HS autograft vs Allograft

We conducted a secondary analysis of second ACL reconstructions (BPTB autograft vs HS autograft vs Allograft). Clinical effectiveness was similar for all options so the analysis was dominated by the costs.

2) Graft prices from Genuario et al (2012) paper

Different graft prices were reported in the Genuario et al[178] paper in US $ in presumably 2010 prices. We converted these costs into UK £ in 2016 prices using the World Bank gross domestic product (GDP) deflators[191] and the purchasing power parity (PPP) measures. [192] The costs for an allograft was £4,412, a HS autograft was £3,223 and a BPTB autograft was £3,856. Having an allograft as a primary ACL reconstruction is more costly and very slightly less effective than having a HS autograft as a primary ACL reconstruction: that is, HS autografts dominated allografts (see Table 22).

Table 22: Sensitivity analyses using graft prices from Genuario et al - discounted results

Procedure	Total mean costs £	Total mean QALYs	Incremental costs	Incremental QALYs	ICER
HS autograft	£3,558	2.6980	-	-	-
Allograft	£4,864	2.6953	£1,305	-0.0026	Dominated

The costs of the allografts used in this sensitivity analysis were taken from the Genuario 2012 study, in which total costs were higher when allograft were used. This cost difference was similar to those reported by Barrera Oro and colleagues (2011 [180]) with a differential supply cost of about $1,400 (the allograft cost was $1,510) and by Cooper and Kaeding [179] with a difference of $1,123. However, Cole and colleagues [183] reported that ACL reconstruction with BPTB autografts cost about $1,000 more than allografts, due to the greater operating theatre time cost of harvesting the autograft and more overnight stays after autograft harvest, even though the supply costs were greater with allografts. Note this latter study used hospital charges and not actual costs.

Conclusion

Given the similarity in outcomes, if there is no reason to prefer an allograft, autografts are more cost-effective.

The results of the cost-effectiveness analysis fit with clinical consensus. A carefully produced consensus document from Italy showed that few surgeons would recommend allografts in primary ACL reconstruction, though in older patients (over 50) there was more support (about half) for using allografts.[195]

3. Allografts in reconstruction of the posterior cruciate ligament

Summary

The available evidence does not show any significant difference in clinical effectiveness between autografts and allografts. Given that, we have provided only a cost analysis, which shows that allografts are most costly. So if an autograft is available, and if there is no clinical reason to prefer an allograft, then on cost grounds, autografts should be preferred. However there will be situations where an allograft might be preferred.

Introduction

Pache and colleagues from the Steadman group[196] provide a useful overview of the PCL and its functions, noting that its function is to stop the femur from sliding too far forward on the tibia, and that it consists of two bundles, a larger anterolateral bundle (ALB) and a smaller posteromedial bundle (PMB). Injuries occur during sports such as soccer and rugby, and also in road traffic accidents, when the flexed knee hits the dashboard and the tibia is displaced backwards.

PCL ruptures are much less common than ACL ruptures (about 10% of ACL numbers) and allografts are commonly used, partly because PCL rupture may be part of a multi-ligament problem. Multi-ligament injuries are an example of a scenario in which allografts become necessary due to a lack of graft availability. Such situations do need to be considered when assessing these results, as for the remainder of this report it is assumed that the PCL is an isolated injury, and that both autografts and allografts are available and a choice can be made between them.

The PCL has much more capacity for healing that the ACL, and many PCL ruptures are treated conservatively, especially if the rupture is partial. Repairs can be single bundle of ALB only, of double bundle of both. Pache et al[196] prefer double bundle repairs. They note previous single bundle repair studies that reported that though results were mostly good, many patients were left with posterior laxity which was associated with OA in later years. An earlier systematic review by Chahla et al [197] used data from 441 patients in 11 studies (mostly not achieving good quality scores, only three were RCTs) to compare the results of double and single bundle repairs. Both methods improved knee stability and patient outcomes, but double bundle gave better posterior stability and IKDC scores.

Evidence

A systematic review by Hudgens and colleagues from the Mayo Clinic[198] included 19 studies, of which five were on allografts, 12 on autografts and two (Wang 2004[199] and Ahn 2005 [200]) compared the grafts. Hudgens et al summarised the advantages of allografts as: shorter operation time, avoidance of donor site morbidity, and a range of graft length and thickness. Disadvantages include deleterious effects on graft strength from sterilisation methods, costs, problems with availability, and a theoretical risk of disease transmission. Disadvantages of autografts included graft size limitations, and the effects of harvesting – increased theatre time, graft site infection, and donor site pain. Hudgens et al note the scarcity of comparative data but conclude that both grafts give satisfactory results.

Tian et al 2017[201] provide a meta-analysis of autograft and allografts in PCL reconstruction but include only five studies, the RCT by Li et al[158], and CCTs by Ahn[200], Li 2015[202], Sun[159] and Wang 2014[199], some of which we would exclude. Ahn 2005 had only 18 patients in each group so is an exclusion according to our protocol – we exclude studies with fewer than 20 patients.

Tian et al conclude that there is insufficient evidence to say whether autografts or allografts are better.

Systematic reviews that were identified in our searches were used as a source of primary studies. We included seven prospective studies of allografts in posterior cruciate ligament (PCL) reconstruction (Li 2014,[203] Yoon 2011,[204] Wang 2004,[199] Min 2011,[205] Min 2011,[205] Spiridonov 2011,[206] Lim 2010,[207] Yoon 2005[208]). We excluded Sun 2015 [159] because grafts were irradiated. We excluded Ahn et al[200] because of numbers. There was a range of study designs, with two RCTs, one controlled clinical trial (CCT) and four single arm before and after studies. Study characteristics and baseline characteristics of the participants are summarised below (see Table 23). The risk of selection bias in the RCTs was unclear, and was high in the CCT. The quality of the non-randomised studies was fair in two studies (Spiridonov et al, 2011[206] Lim et al 2010[207]) and poor in two studies (Min et al 2011[205] Yoon et al, 2005[208]). The overall quality of each study is reported within the results below. Not all are relevant to our primary question.

Table 23: Prospective PCL studies included in this review

Author	Intervention details	Study Design
Li et al, 2014[203]	PCL Allograft (Single bundle vs double bundle)	RCT (comparison not relevant to review)
Yoon et al, 2011[204]	PCL Allograft (single bundle vs double bundle)	RCT (comparison not relevant to review)
Wang et al, 2004[199]	PCL Allograft vs Autograft	CCT
Cooper et al 2004[163]	PCL allograft vs autograft	CCT
Min et al, 2011[205]	PCL Allograft	Before and After
Spiridonov et al, 2011[206]	PCL Allograft	Before and After
Lim et al, 2010[207]	PCL Allograft	Before and After
Yoon et al, 2005[208]	PCL Allograft	Before and After

Sample sizes in the included studies ranged from 21 to 60 participants, with a total of 273 between them (241 having allografts), although numbers analysed were lower. Mean length of follow-up ranged from 2 years to 4.3 years. Four studies were undertaken in South Korea, one in China, one in Taiwan and one in the USA. Eligibility criteria or indication for the allograft differed between the studies. In four studies between 19% and 82% of participants had concurrent procedures, which were not reported by three studies. The mean ages of participants ranged between 23.5 years and 36 years and males represented between 68% and 90.5% of participants (see Table 24).

Table 24: Study and baseline characteristics: PCL reconstruction

Study	Indication / inclusion criteria and procedures	Concomitant procedures	Baselines
Li et al, 2014[203] **Country:** China **Study Design**: RCT (comparison not relevant to review) **Follow-up duration**: SB 28.7 months (SD 3.0); DB 30.4 months (SD 5.1) **Sample size:** 50 (SB 25, DB 25)	Isolated posterior knee instability grade II to III, 2007 – 2009. Two groups double-bundle (DB) technique and single-bundle (SB) technique compared	Not reported	**Age[a] :** SB 25.1 (SD 2.6); DB 23.5 (SD 5.2) **% male:** SB 68.2; DB 75.0
Yoon et al, 2011[204] **Country:** Korea **Study Design**: RCT (comparison not relevant to review) **Follow-up duration**: SB 31 months (range 24-42); DB 33 months (range 24-43) **Sample size**: 60 (SB 30, DB 30)	Arthroscopic PCL reconstruction for an isolated PCL tear, 2005-2007. Two groups double-bundle (DB) technique and single-bundle (SB) technique compared	Not reported	**Age[a] :** SB 28.5 (17-47); DB 27.4 (18-46) **% male:** SB 80.0; DB 89.3
Wang et al, 2004[199] **Country:** Taiwan **Study Design**: CCT **Follow-up duration**: mean 34 months (SD 10, range 24-71) **Sample size:** 55 (23 allograft, 32 autograft)	Indications included pain and instability as a result of high-energy posterior cruciate ligament injury with failure of conservative treatments for 3 months. 1997-2001.	50% had meniscectomies, meniscus repairs, and/or debridement	**Age[a] :** Allograft 30 (SD 12); autograft 29 (12) **% male:** Allograft 69.6; autograft 78.1
Min et al, 2011[205] **Country:** Korea **Study design:** Before and after study (authors' definition case series) **Follow-up duration**: 51.7 months (range, 25-73 months). **Sample size:** 21	Indication was painful instability above daily activities in active patients and a PCL injury with >10 mm side-to-side difference. All had isolated PCL rupture with or without meniscal injury and grade III posterior instability. 2003-2007.	Partial meniscectomy in 19%.	**Age[a] :** 35.6 (18-54) **% male:** 90.5
Spiridonov et al, 2011[206] **Country:** USA **Study design:** before and after study **Follow-up duration**: 2.5 (2.0 – 4.3) years	Evidence of an unstable knee with acute multiple ligament injuries, a chronic PCL tear that had not responded to non-operative treatment, or a chronic combined injury of	10.3% had initial proximal tibial biplanar osteotomy. 82% had combined procedures (PCL	**Age[a] :** 33 (15 – 62) **% male:** 84.6

Sample size: 39	the PCL and posterolateral or medial and/or posteromedial ligaments of the knee were enrolled. Indication grade-III isolated or combined PCL tears. 2005 – 2008.	with range of medial knee reconstruction; PLC reconstruction, ACL). .	
Lim et al, 2010[207] **Country:** Korea **Study design:** Before and after study **Follow-up duration**: 33 (24-60) months **Sample size**: 22	Pain or instability during daily activities despite non-operative treatment for more than 6 months, and a PCL injury with more than an 8 mm side-to-side difference in posterior displacement.	Not reported	**Age**[a] **:** 36 (18-59) **% male:** 86.4
Yoon et al, 2005[208] **Country:** Korea **Study design**[a]**:** before-after study (author's description case series) **Follow-up duration**: 25 months (range 12-48) **Sample size:** 26 (27 knees)	Underwent arthroscopic double-bundle PCL augmentation using split Achilles allograft 1999-2002. All had contact mechanisms of injury.	35% with combined ACL deficiency had arthroscopic reconstruction using tibialis anterior allograft, 57.7% meniscectomy or meniscorrhaphy.	**Age**[a] **:** 27.9 (17-43) **% male:** 73.1
Cooper et al 2004 **Country USA** 1991-2001 **Design:** Comparison of results after 16 autografts and 25 allografts. 35 primary repairs and 6 revisions Mean follow-up 39 months, minimum 24 months	Single bundle using BPTB grafts. Wider grafts used allografts. Some allografts were irradiated with "low dose" <1.8 rads but number treated and results are not given separately	85% had concomitant other ligament repair.	**Average age 28** **76% male**
Yantai, China **Design.**Comparison of 36 patients having autografts and 35 having allografts	Arthroscopic reconstructions		**Mean age 32.** **75% male**

[a]mean (range) unless stated otherwise;

Results - Failure and survival

None of the studies reported allograft failure rates or survival of the allograft. Spiridonov et al 2011[206] reported a rate of implant removal of 7.7% at a mean of 2.5 years follow-up. Li et al 2014[203] stated that no participants required additional surgery because of recurrent or residual symptoms.

Results – progression of arthritis

No studies reported this outcome

Results – functional outcomes

Six of the studies reported the Lysholm knee score. (Wang 2004;[199] Li 2014;[203] Yoon 2011;[204] Min 2011;[205] Lim 2010;[207] Yoon 2005[208]) In the CCT by Wang et al 2004[199] (high risk of selection bias) there was no statistically significant difference between the allograft group and the autograft group at endpoint (Table 25). All other studies demonstrated a statistically significant improvement in Lysholm score at endpoint. Sample sizes were small and no studies were of low risk of bias / good quality; Lim et al 2010[207] was of fair quality.

Table 25: Lysholm knee score, PCL reconstruction

Lysholm Knee score at final endpoint, mean (SD) unless stated			
Wang 2004[199] **High ROB**	**Allograft Group, n=23**	**Autograft, n= 32**	**P-value**
Endpoint value	92.3 (6.8)	87.8 (9.6)	0.077
Li 2014[203] **Unclear ROB**	**Single-bundle allograft, n=22**	**Double bundle allograft, n=24**	**P-value**
Baseline value Endpoint value P-value	63.1 (3.8) 88.0 (4.2) p<0.05 [a]	64.6 (4.3) 89.8 (3.8) p<0.05 [a]	 NA
Yoon 2011[204] **Unclear ROB**	**Single-bundle allograft, n=25**	**Double bundle allograft, n=28**	**P-value**
Median (Range) Baseline value Endpoint value P-value	 64 (41-73) 89 (71-99) p<0.001	 62 (43-71) 91 (76-100) p<0.001	 NA
Min 2011[205] Poor quality	**Allograft, n=21**		
Mean (Range) Baseline value Endpoint value P-value	 52.2 (42-66)[b] 78 (56-92)[b] <0.001		
Lim 2010[207] Fair quality	**Allograft, n=22**		
Median (Range) Baseline value Endpoint value P-value	 64 (50-75) 88 (82–96)[c] <0.001		
Yoon 2005[208] Poor quality	**Allograft, n=26**		
Baseline value Endpoint value P-value	59.5 91.8 p<0.05		

[a] p value between baseline and 24 months after surgery, data presented are for final follow-up.

[b]rates different in the abstract, which states was 53 (SD 5.3), range 34-68 preoperatively and 83.5 (SD 13), range 61-97 at follow-up of mean 49.2 months (range 25-73)

[c]Also states 89.9 (SD 6.5).

Four studies (Wang 2004[199] Li 2014[203] Yoon 2011[204] Lim 2010[207]) reported the Tegner score (Table 26). There was no statistically significant difference between allografts and autografts in the Wang et al 2004 study. All other studies found a statistically significant improvement in Tegner score at follow-up, although no studies were of low risk of bias / good quality and sample sizes were small.

Table 26: Tegner scores, PCL reconstruction

Tegner score at final endpoint, mean (SD) unless stated			
Wang 2004[199] **High ROB**	**Allograft Group, n=23**	**Autograft, n= 32**	**P-value**
Endpoint value	4.70 (1.66)	4.73 (1.66)	0.976
Li 2014[203] **Unclear ROB**	**Single-bundle allograft, n=22**	**Double bundle allograft, n=24**	**P-value**
Baseline value Endpoint value P-value	3.1 (0.6) 6.2 (0.9) p<0.05[a]	3.3 (1.0) 6.8 (1.2) p<0.05 [a]	 NA
Yoon 2011[204] **Unclear ROB**	**Single-bundle allograft, n=25**	**Double bundle allograft, n=28**	**P-value**
Median (Range) Baseline value Endpoint value P-value	 2 (1-3) 6 (4-7) p<0.001	 2 (1-3) 6 (4-7) p<0.001	 NA
Lim 2010[207] Fair quality	**Allograft, n=22**		
Median (Range) Baseline value Endpoint value P-value	 3 (2-5) 6 (3-9)[b] <0.01		

[a] p value between baseline and 24 months after surgery, data presented are for final follow-up.
[b]states mean, reviewer assumed this is median as per the other outcomes.

Three studies assessed the IKDC subjective score (Li 2014[203] Yoon 2011[204] Spiridonov 2011[206]). As seen in Table 27, in the two studies that compared outcomes with baseline, a statistically significant improvement was seen with allografts.

Table 27: IKDC subjective, PCL reconstruction

IKDC subjective at final endpoint, mean (SD) unless stated			
Li 2014[203] **Unclear ROB**	**Single-bundle allograft, n=22**	**Double bundle allograft, n=24**	**P-value**
Endpoint value	65.5 (7.8)	71.6 (6.7)	NA
Yoon 2011[204] **Unclear ROB**	**Single-bundle allograft, n=25**	**Double bundle allograft, n=28**	**P-value**
Median (Range) Baseline value Endpoint value P-value	 40.2 (27.6-46.0) 79.3 (59.8-88.5) p<0.001	 39.1 (27.6-48.3) 81.7 (65.5-88.5) p<0.001	 NA
Spiridonov 2011[206] Fair quality	**Allograft, n=39**		
Baseline value Endpoint value P-value	39.3 (18.8) 74.3 (23.1), n=31 <0.0001		
Cooper 2004	Allografts 25, autografts 16.		
Baselines all severely abnormal based on stability	Average final score 75 (20-100) with better scores with allografts (xx vs ZZ ADD) P <0.05, but overall results similar, and note not an RCT and different graft thicknesses. EXPAND		

Results – quality of life

No studies of PCL reported quality of life.

Adverse events

Of the seven studies only three reported any specific complications or adverse events and rates were generally low. Yoon et al 2011[204] reported postoperative limited range of motion in 4% and 7% of participants in the single-bundle allograft and double-bundle allograft groups respectively. Wang et al 2004[199] reported one complication (4.3%, organism isolated from wound but no clinical infection) occurred in the allograft group and seven (21.9%; two infections, four donor site pain) in the autograft group. Min et al 2011[205] reported arthrofibrosis in 4.8% and irritation leading to tibial screw removal in 19% of their allograft cases. Three other studies reported no major neurologic, vascular, or wound complications (Li 2014[203]); no intraoperative neurovascular injuries, deep vein thrombosis or infections (Spiridonov 2011[206]) or no complications (Lim 2010[207]) respectively. Yoon et al 2005[208] did not report adverse events.

Results – subgroups

Spiridonov et al 2011[206] which was of fair quality, reported subgroups for those having isolated procedures (n=7) and those having combined procedures (n=32). Statistically significant improvements were seen in both groups on the modified Cincinnati score and IKDC subjective score. No comparison between subgroups was reported. It is unlikely that the study was powered for these subgroup analyses.

Cooper and Stewart [163] 2004 did report that posterior laxity was better after primary repair than after revision PCL repair, but had only six revisions.

Other studies

An English abstract of a trial published in Chinese by Yang et al [209] was obtained. 100 patients were randomised to allografts or autografts for anterior or posterior cruciate ligament repairs. No differences between graft types were found. Results for anterior and posterior were not given separately.

We identified a recent review by Belk et al 2017 [210], but it contained only 5 trials, and although the title mentioned autograft versus allograft in PCL reconstruction, some of the included studies provided little information. One (Kim et al 2000) had two groups, one all autografts, and the other 75% autografts. Two of the other studies used irradiated allografts, and a fourth study had numbers below our threshold of 20 per arm.

Jung et al[211] compared differences in results in men and women after PCL reconstructions, in which about a third had allografts. However the allograft results were not provided separately. They found that reduction of tibial laxity was slightly greater in women.

Khakha and colleagues[212] provide a single case study of the use of a parental allograft for PCL repair an 11-year old boy. This may be considered in cases where allografts are not available, but given the similar clinical results for allograft and autograft reconstruction, it seems unnecessary to harvest from a parent donor when good allograft options are available.

Cost-effectiveness of posterior cruciate ligament (PCL) reconstruction

The original aim of the cost-effectiveness analysis was to determine whether an allograft or an autograft is the more cost-effective option for patients requiring a PCL reconstruction. Isolated PCL injuries are less common and usually less of a problem for patients in that they often respond to physiotherapy, but some cases do cause problems despite conservative care and require surgery. We start from the position that surgery is required, so conservative care is not included in the model.

Patients requiring a PCL reconstruction can have a number of outcomes:

- Permanent success – where symptoms are relieved;
- Failure – followed by another reconstruction;
- Failure - but a patient may decide against another reconstruction and have conservative care, including physiotherapy, instead.

This section describes the model structure, the parameters used within the model (probabilities, resource use, costs and utilities), the assumptions made within the model and the results.

Model structure

A decision tree model was developed within Microsoft Excel® and was considered the most appropriate choice as reconstruction is usually successful and most patients return to a functioning knee after reconstructive surgery. The starting point for the economic model is at the point where the decision is made to do PCL reconstruction. The clinical pathways were developed using information from the published literature and clinical expert opinion. Figure 7 shows the different clinical pathways.

The pathway assumes that a patient needing PCL reconstruction either has an allograft or a hamstring (HS) autograft as a first reconstruction. After the first PCL reconstruction, there are two main options:

- Reconstruction was successful with symptoms resolve and full function restored
- Reconstruction failed with symptoms not resolving and patients can opt to have another reconstruction or conservative care. Conservative care consists of an orthopaedic consultation visit post-operation and eight hospital physiotherapy sessions.

Allograft pathway

Patients in whom the first allograft reconstruction fails, can either have another allograft reconstruction or conservative care. The second allograft reconstruction can succeed or fail. If the second allograft reconstruction fails, patients can either have another reconstruction or conservative care. For those that have a third and final allograft reconstruction, this can either succeed or fail. After a third failed allograft reconstruction, we have assumed that there only option is conservative care.

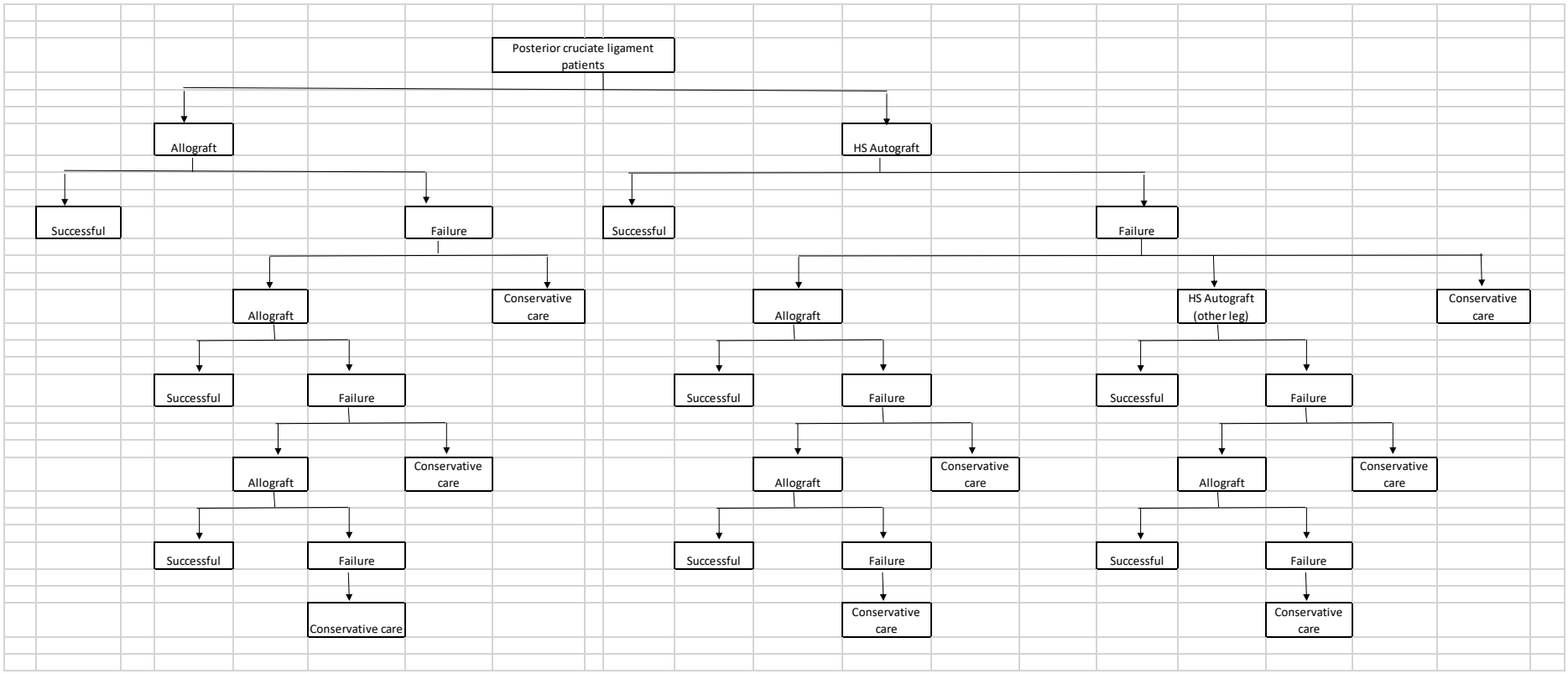

Figure 7: PCL clinical pathway

Hamstring autograft pathway

For those that have failed the first HS autograft reconstruction, there are three choices:

- An allograft
- HS autograft (from other leg)
- Conservative care

The allograft can succeed or fail. If it fails, patients can have another allograft or conservative care. If the third allograft reconstruction fails, then we have assumed that the only option for the patient is conservative care. (We have assumed, simplistically, that if surgeons starts with an allograft, they will continue with allografts.)

An HS autograft from the other leg (option 2) can succeed or fail. After failure, the options are either an allograft or conservative care. If the allograft fails, then we have assumed that the only option is conservative care.

A simplified version of the pathways is shown in Table 28.

Table 28: Different combinations for PCL reconstruction

1st line	2nd line	3rd line
Allograft	Allograft	Allograft
Hamstring autograft	Hamstring autograft (other leg)	Allograft
	Allograft	Allograft

Base-case analysis and modelling issues

For the base-case analysis, we have adopted a three-year time horizon. We have not differentiated by gender or taken into account mortality. The starting age for a patient is 25 years. The analysis is conducted from the perspective of the UK National Health Service (NHS) and personal social services (PSS). All costs are in pounds sterling (£) in 2016/2017 prices. Health outcomes are measured in quality-adjusted life years (QALYs). Results are expressed as incremental cost-effectiveness ratio (ICER) more commonly known as an incremental cost per QALY gained. An annual discount rate of 3.5% is applied to both costs and outcomes in line with recommended guidelines.[185]

Cost-effectiveness analysis is only worthwhile if there are differences in clinical effectiveness. If there are none reported, we cannot generate utility data and QALYs. We developed a model for analysis but given the paucity of evidence comparing allografts and autografts, and the lack of any significant differences in the available studies and analyses, we have not undertaken any modelling analyses. Therefore, this section now presents a simple cost analysis comparing the cost of allografts versus autografts for PCL reconstruction.

Resource use and costs

All unit costs reported in Table 29 are presented in pounds sterling (£) in 2016/17 prices. The cost of the allograft (£2,400) was obtained from the NHS Tissue Services price list for 2018/19 and was based on an average price of posterior tibialis tendon.[189] We have not accounted for the price difference between the two financial years. There is no cost for the graft in the HS autograft arm, except a little extra theatre time (but the procedure code will not change). We have included the cost of the procedure, three consultant led follow-up clinics, eight physiotherapy sessions and the

cost of analgesics (paracetamol and ibuprofen). We have assumed that a second or third PCL revision would cost the same as a first reconstruction (see Table 20).

We have also assumed that 0.3% of all reconstructions will get infections based on a recent ACL study.[190] The cost of infections was obtained from the Genuario et al[178] paper in US $ in presumably 2010 prices. We converted these costs into UK £ in 2017 prices using the World Bank gross domestic product (GDP) deflators[191] and the purchasing power parity (PPP) measures.[192] The cost of treatment for an infection included the cost of requiring debridement, irrigation, and antibiotics started intravenously with one-week hospital admission then continued for a further 5 weeks.[178]

Conservative care costs were based on a follow-up consultant led outpatient clinic and eight physiotherapy sessions. Any costs not in 2016/2017 prices have been uplifted using the Hospital and Community Health Services (HCHS) index.[87]

Table 29: Resource use and costs for PCL reconstruction

Resource use	Unit cost (£)	Source
Graft type		
Allograft	£2,400	Tissue bank[189]
Procedure		
Intermediate knee procedures for non-trauma, 19 years and over (HRG code: HN24C)	£1,642	NHS reference costs 2015-16[86]
Other related costs		
Three non-admitted consultant led outpatient follow-up attendance (HRG code: WF01A)		
8 hospital physiotherapy sessions (30 mins)	£336	NHS reference costs 2015-16[86]
Paracetamol (two tablets twice a day per year)		
Ibuprofen (one tablet a day per year)	£132	UCHSC 2017[87]
Total costs	£23.21	BNF 2016-17[88]
Allograft	£12.47	BNF 2016-17[88]
HS autograft		
BPTB autograft	£4,395	
	£2,145	
	£2,145	
Infection		
Infections	£7,761	Genuario et al (2012)[178]
Conservative care		
One consultant led outpatient follow-up attendance (HRG code: WF01A)	£112	NHS reference costs 2015-16[86]
8 hospital physiotherapy sessions (30 mins)	£132	UCHSC 2016[194]

Results

Table 30: Base-case discounted results, PCL reconstruction

Procedure	Total mean costs £	Incremental costs
HS autograft	£2,426	-
Allograft	£4,881	£2,455

Table 30 shows the base-case discounted cost results. Having an allograft as a primary ACL reconstruction is more costly (£2,455 more) than having a HS autograft as a primary ACL reconstruction. The main cost driver for this result was the cost of the graft.

There are some uncertainties. We include simple analgesics, but some patients may have pain severe enough to require opiate analgesics such as tramadol, and addiction may be a risk [213]

Conclusion

The decision therefore depends on costs. Given the extra cost of allografts, they do not seem justified if autografts are available, and if there is no clinical reason to prefer an allograft. However PCL injuries often occur as part of multi-ligament knee injuries, where availability of suitable autografts may be an issue.

Chapter 4: Meniscal allograft transplantation

Summary

It is generally accepted that meniscectomy leads to osteoarthritis, but the speed of progression varies amongst studies. Damage to articular cartilage at the time of the meniscal injury is common, so it may sometimes be difficult to know how much of the OA to attribute to meniscectomy. Meniscal damage without meniscectomy is associated with later OA. The prevalence of OA at any time period depends on how it is diagnosed (radiological, MRI, symptomatic). (This review is concerned with meniscectomy after trauma, often in mid-teens to mid-twenties, often related to sport, and not with the degenerative meniscal damage seen in older people.)

The evidence on whether MAT protects is more difficult. A systematic review by Smith and colleagues [214] concluded that;

"There is some evidence to support the hypothesis that meniscal allograft transplantation reduces the progression of osteoarthritis, although it is unlikely to be as effective as the native meniscus. If this is proven, there may be a role for prophylactic meniscal allograft transplantation in selected patients. Well-designed randomised controlled trials are needed to further test this hypothesis."

MAT relieves symptoms in those who have them after meniscectomy (typically developing at a mean of seven years after the meniscectomy), and thereby improves quality of life. However the proportion of patients that should have MAT after meniscectomy is uncertain, even if cost was not a consideration. Our estimate is 10-20%, but others might suggest a higher figure, and one small study even inserted MATs prophylactically at time of meniscectomy.

MAT is clinically effective in relieving symptoms, as measured by scores such as KOOS, IKDC, Lysholm and Tegner. However, most studies had no matched controls receiving conservative care, so the undoubted benefits of MAT over conservative care (including analgesia, physiotherapy) cannot be quantified, making cost-effectiveness analysis problematic. It is not enough to say "MAT works". In cost-effectiveness analysis it is the effect size compared to the comparator that matters.

Whether it reduces or delays progression to advanced OA, is less certain. If MAT reduced or delayed knee replacement, that would result in savings to offset the cost of MAT. A cost-effectiveness analysis by Bendich and colleagues[215] estimated that MAT would need to reduce progression to severe OA by 31% to be cost-effective in their base case of someone aged 30, BMI 20 and no OA. In other scenarios, a smaller reduction in progression would make MAT cost-effective.
So given the current lack of evidence on chondroprotection, we cannot say that MAT is definitely cost-effective, but it is likely to be so in some groups. It may be cost-effective on relief of symptoms alone, without factoring in delay in or avoidance of, later arthroplasty.

One high priority for research is for ways of identifying the 10-20% of people who do worst after meniscectomy.

For debate

The people who get MAT after meniscectomy may be a small subset, perhaps only 10-20% (*can ESSKA members provide data*?) of all having meniscectomy.

Our impression is that a second MAT in the same compartment is uncommon, and that there is little data. However if a first MAT in a young person lasted for, say, 10 years, providing symptomatic

relief, there would seem to be a case for a repeat MAT, perhaps as an interim intervention pending knee arthroplasty. (If the relief of symptoms improved quality of life by 0.2 on a scale of 0 to 1.0, benefits over 10 years would equate to 2 QALYs – NICE would regard that as being worth £20,000 to £30,000.)

A subgroup of patients get significant problems after meniscectomy, and MAT is indicated. Can we identify their characteristics in order to look for a matching group that don't get MAT? Without a data from a matching group, we can't quantify the benefits of MAT over no-MAT.

Some authorities recommend MAT only in knees with little or no degenerative change. But the Coventry study [216] [217] showed benefits in people with advanced "bone on bone" change, and because they are worse off to being with, they have more to gain, and in them, MAT might actually be more cost-effective. (We have not examined this question.)

Questions

There are three issues to be considered;

- Does meniscectomy lead to early osteoarthritis?
- Does MAT prevent or delay OA after meniscectomy?
- Is MAT an effective way of relieving continuing symptoms after meniscectomy?

Introduction

The meniscal cartilages are fibrocartilaginous structures lying between the femoral condyles and the tibial plateaux. They have a number of functions including load-bearing and shock absorption. The meniscal cartilages spread the weight-bearing forces in the knee, thereby preserving the articular cartilage on femoral condyles and tibial plateau. The lateral meniscus is thought to carry approximately 70% of the load in its compartment, and the medial one 50%, when the leg is straight. Hannon and colleagues [218] and the IMREF 2015 Consensus statement [219] have provided reviews of the history of meniscectomy and of meniscal allograft transplantation (MAT).

Meniscal injury and subsequent meniscectomy is thought to lead to early osteoarthritis (OA) because of increased stress on the central articular cartilage. The articular cartilage under the menisci is thinner than on other parts of the tibial plateau [220] and so the sub-meniscal region is more at risk of OA if the meniscus is removed. Because acute meniscal injuries often occur in sport, those afflicted are often young. For example in the case series of 63 patients reported by Cameron and Saha 1997 [221] the average age at meniscectomy was 24. An even younger cohort was reported by Pengas et al (from the 1960s and 1970s) [222] in which 313 patients with mean age 16 (range 10-19) at meniscectomy were followed up for about 40 years (mean age at assessment 57, range 43-67). OA was found in 87% of meniscectomised knees but in only 18% of non-operated knees. All were either symptomatic (mean KOOS 70) or (13%) had had knee replacement.

Acute meniscal injuries due to trauma in young people should be distinguished from the degenerative meniscal lesions that are common in older people – 25% in age range 50-59 years, increasing to 45% in those aged 70-79. The ESSKA 2016 consensus [223] was that meniscectomy should not be a first line treatment in degenerative meniscal lesions.

Several authors (Ahn[224] Alentron-Geli [225], Cole[51], Jauregito[226]) have asserted that meniscectomy leads to OA but the evidence is mixed for several reasons. One is duration of follow-up. Jackson [227] reviewed 577 knees after meniscectomy and compared them with the patients' other knees.

Definite radiographic degenerative changes were much more common in meniscectomised knees (21% versus 5%) but took time to develop, being seen in 22% (control knees 4%) at under 20 years, 53% at 20-29 years (controls 13%) and 67% at 30-40 years. However only about half of those with radiological degeneration had painful knees.

Given what is known about the functions of the meniscus, meniscectomy would be expected to increase the risk of osteoarthritis (OA). However, for assessing the cost-effectiveness of MAT in reducing OA, we need to know the risks of OA after meniscectomy with and without MAT.

The systematic review by Smith and colleagues [214] concluded that in 35 studies with mean follow-up 5.9 years, there was good evidence that MAT improved symptoms after meniscectomy, but that there was insufficient evidence as to whether MAT would be chondroprotective. Smith et al noted the lack of randomised controlled trials (RCTs) of MAT versus conservative care. It would be much easier to quantify the effect of MAT on OA if data were available on matched patients that did not have MAT.

One issue is that meniscal injuries are often associated with damage to articular cartilage, so that later OA may be related to the articular cartilage damage as well as, or rather than, meniscectomy. So OA in a meniscectomised patient may not be due entirely to the absence of a meniscus. However in the study by Roos et al [228], 19% had evidence of articular cartilage damage at the time of meniscectomy but 71% had OA in the knees 21 years later, with 48% having Kellgren and Lawrence (KL) grades of 2 or worse. Roos et al compared the prevalence of OA in meniscectomised knees to those in a population-based control group, in which any OA was seen in 18% and KL grade 2 or worse in 7%. Unfortunately the response rate amongst the invited controls was under 40%, and those who responded may have had more knee pathology, and hence interest, than those who did not. Roos et al make a useful point about using contralateral knees in meniscectomised patients for control purposes, because the other knees had higher rates of OA than the control group, relative risk (RR) 1.5 for any OA. So it could be argued that using contralateral knees as controls may under-estimate the effect of meniscectomy. Conversely if the contralateral knees have an increased risk of OA, some of the OA seen in the meniscectomised knee may not be due to the meniscectomy. It is known that OA in one knee causes 'overloading' of the other side (that is, OA in the contralateral knee may be blamed on OA in the meniscectomised joint), but not the degree to which this is important, over and above a person's pre-determined genetic tendency to OA. [229]

Another issue is how OA is determined – radiological or symptomatic. In a study of elite American football players with mean age 23 by Smith et al [230], OA was defined as moderate to severe non-focal articular cartilage loss on MRI or joint space narrowing on plain radiographs. They were selected for imaging because they had had previous surgery or had knee symptoms. OA was seen in 15%, but in 4% of those with no previous knee surgery and in 27% of those who had had partial meniscectomy. Mean BMI was 32. Their symptom scores were not reported, but all were still functioning at a high level.

Paradowski et al [231] also assessed OA by radiology, defining it as joint space narrowing or the presence of osteophytes, equivalent to KL stage 2, in cohorts from 1973, 1978 and 1983-85. Follow-up varied in duration, as did the type of meniscectomy, with total or subtotal in the early years, but with more (35%) partial meniscectomy in later years. Mean age at meniscectomy was 35 years, and at follow-up 60 (range 34-85) years. Radiographs of the other knees were also taken. The prevalence

of tibio-femoral OA at last follow-up was 68% in the meniscectomised group and 36% in the other knees (some of which may have had other surgery).

Claes et al [232] carried out a meta-analysis of 16 studies of OA after anterior cruciate ligament (ACL) reconstruction, with a minimum follow-up of 10 years, published before October 2010. Eleven studies with 614 patients were used for analysis of the effect of meniscectomy. There was considerable heterogeneity amongst studies, but this was in effect size not direction. The overall OR for OA after meniscectomy was 3.5 (95% confidence interval (CI) 2.6-4.9), with OA seen in 50% after meniscectomy and in 16% in control knees.

Other variables that affect the incidence of OA include which cartilage was removed, and whether there is varus or valgus mal-alignment. Allen et al 1894 [233] followed up 230 patients who could be traced out of a series of 428 who had meniscectomy in the years 1958-1970. Some had died but 210 (49% of the original cohort) were reviewed 10 to 22 years post-meniscectomy. Age at meniscectomy ranged from 13 to 67 years and at follow-up from 29 to 85 years. Radiographs were obtained of both knees. Over half the meniscectomised knees were clinically normal at mean follow-up of 17 years, but radiological signs of OA were seen in 18% of meniscectomised knees compared to 5% of the control knees. OA was more frequent after lateral meniscectomy than medial, presumably because the lateral meniscus covers more of the tibial plateau. After lateral meniscectomy, OA was more common in valgus knees, and after medial meniscectomy, OA was more common in varus knees.

Another reason is the presence of other knee problems such as cruciate ligament tears. Burks et al [234] reported the 15-year results after partial meniscectomy, comparing the knees operated on with the other knee in each patient. There was little difference clinically or radiologically in patients with normal ACLs, but those with ACL tears had significantly worse radiological grades.

The lateral meniscus is normally crescent shaped but is occasionally larger, even a complete circle. This is known as a discoid cartilage, and may be more prone to injury. Ramme et al [235] compared the cost-effectiveness of MAT and partial meniscectomy in young women with torn discoid lateral meniscus and concluded that MAT was cost-effective.

Meniscectomy can be total or partial. Andersson-Molina et al 2002 [236] noted radiographic changes 14 years after meniscectomy, including joint space narrowing in 13 of 18 patients after total meniscectomy, but only 6 of 18 after partial meniscectomy. Joint space narrowing was seen in 7 patients after total meniscectomy but in only one who had partial meniscectomy. Andersson-Molina et al compared the meniscectomised group with 36 matched controls (from a local football club) with no history of knee injury, none of whom had joint space narrowing. Despite the radiographic changes, about 70% of the meniscectomy group had normal Lysholm scores at 14 years.

Rongen et al [237], using data from the Osteoarthritis Initiative, found that meniscectomy conferred a hazard ratio for OA of 3.03 compared to a matched group that had not had meniscectomy. The meniscectomised group (335 patients) had a higher rate of total knee replacement (TKA) than the controls, 18% versus 11%. However, this study is perhaps not as relevant to this review as some others, because the patients studied were in age range 45-79, so many would have had degenerative change in their menisci rather than acute trauma.

A key question is quantifying the risk of OA after meniscectomy compared to knees that do not have meniscectomy. Table 1 shows some relative risk ratios at different intervals with fair consistency in the relative risks ranging from 3.1 to 5.8.

Table 31: Risk of osteoarthritis after meniscectomy

	OA after meniscectomy	OA no meniscectomy	Relative risks
Duration of follow-up			
10-19 years			
Allen et al [233]	18%	5%	3.6
Jackson et al [238]	23%	4%	5.8
20-29 years			
Jackson et al	53%	13%	4.1
40 years			
Pengas et al [239]	87%	16%	4.8
>10 years			
Claes et al [232]	50	16	3.1

IMREF 2015 consensus (Getgood et al [219])

This consensus statement provides a useful section on the history of MAT, noting that there was once a time when the roles of the menisci were not appreciated. Indeed, they were considered to be a vestigial remnant and "removed without thought". However it was later realised that they had a number of functions, including load-spreading, and preserving the articular cartilage on femoral condyles and tibial plateaux. The consensus notes that meniscectomy increases the risk of osteoarthritis.

The IMREF 2015 statement recommended three main indications for MAT;

- Unicompartmental pain following total or defunctioning subtotal meniscectomy
- As a concomitant procedure to ACL reconstruction in order to prolong the life of ACL reconstruction
- As a concomitant procedure to articular cartilage repair in a meniscus-deficient compartment

However, the IMREF consensus recommended that MAT was not indicated in patients with no meniscus but no symptoms. This could be seen as a problem given that people may be developing OA without symptoms in the early stages. The decision was based on a paucity of evidence of chondroprotective benefit in asymptomatic people, and consideration of the significant re-operation rate after MAT (as high as 35%). Those in the Consensus group who would do MAT in asymptomatic patients (18%), would do so only in the lateral compartment.

Some authorities recommend MAT only in knees with little or no degenerative change.[220]

The aim of the present study was to assess the cost-effectiveness of MAT after meniscectomy. The benefits of MAT could be, firstly relief of symptoms and restoration of quality of life, and secondly, avoidance or delay in the development of symptomatic osteoarthritis and the subsequent need for knee replacement.

Methods

A systematic review of clinical effectiveness was carried out. A number of recent systematic reviews were identified, their quality assessed, and their conclusions summarised. Their inclusions varied because their topics of interest varied. A search for recent studies not included in those reviews was carried out to update them.

Our searches identified studies that were conducted prospectively and studies that used retrospective data analysis. There are potential biases in both study types, however a well-designed prospective study is generally less prone to bias and confounding than a well-designed retrospective study [240]. For example, retrospective studies will often not have accurate information on other risk factors that could influence the outcomes that are important to the study. Additionally, retrospective studies may not deliver the intervention consistently across the study population, and depending on the methods used can be prone to miss out data on eligible participants. Therefore a prospective study is more likely to make precise estimates of outcomes of relevant and for this reason, greater weight was given to prospective studies, with summary details of retrospective studies recorded. It should be noted that some studies that are described by their authors as retrospective, are based on prospective data collection and can be regarded as prospective.

Full details of search strategy are given in Appendix 1, but in brief;

- The databases Ovid Medline, Ovid Embase, Web of Science and the Cochrane Library were searched for articles published from the year 2000 until February 15th 2018. The Medline search strategy and the numbers of records obtained are shown in Appendix 1 to the Supplementary files.
- After February 2018, an auto-alert system was set up to detect new studies, and some were added up to early 2019.
- Titles and abstracts of retrieved studies were screened by two people, with full papers obtained if inclusion or exclusion was uncertain from the abstract
- Standard systematic review methods were used with quality assessment of included studies using standard checklists for both reviews and primary studies, and checking of data extractions by a second reviewer

Data were sought on:

- Quality of life, preferably using a generic preference based measure or a condition-specific measure that could be mapped to a utility measure such as EQ-5D
- Data on failures and reoperations and graft survival
- The development of OA, and the frequency of knee replacement, either unicompartmental or total.
- Data on costs, both short-term (the costs of MAT), medium term (the cost of treatment of both those having MAT and those having non-operative care) and long-term (the costs of OA and arthroplasty)

All included studies were assessed for methodological quality using recommended criteria. The Cochrane risk of bias (ROB) assessment criteria [241] were to be used for RCTs and controlled clinical trials (CCTs). Six possible biases were assessed: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. We assessed performance bias, detection bias and attrition bias separately for outcomes that were considered to be objective (e.g. failure rates) and subjective (e.g quality of life measures). Each criterion was assigned a judgement of “high,” “low” or

"unclear" risk of bias. To establish the overall risk of bias of a study we used the risk of selection bias (generation and concealment of the allocation sequence).

For non-randomised studies we used tools developed by the National Institute for Health, National Heart, Lung and Blood Institute (NIH NHLBI).[242] These tools focus on biases (selection, performance, detection and attrition), confounding, power and strengths of associations between treatments and outcomes. We used the tools for cohort studies (two group comparisons), before and after studies (one group) and case series studies (one group, no before measure). Each question was assigned a response of 'yes', 'no', 'can't determine', 'not reported' or 'not applicable'. The study was then assessed for overall quality (good, fair, poor) based on the responses to the individual questions. Some criteria may be more important than others, however, for efficiency we used the number of "yes" responses as a general rule of thumb to judge the overall quality of a study as follows:

- For before and after studies (10 core questions): Good 8-10, Fair 5-7, Poor <5
- For cohort studies (14 questions), Good 10-14, Fair 7-9, Poor < 7
- For case series (9 questions), Good 8-9, Fair 5-7, Poor <5.

Results

The quality assessment, results and conclusion of selected reviews are shown in Tables 32 and 33.

Thirty-seven papers from 18 studies of MAT were included (Table 34).

Meniscal cartilage replacement – recent reviews

Table 32: Quality assessment using NIH criteria

Review	Focused question	Eligibility criteria	Searches	Dual review	Validity	Study details	Publication bias	Heterogeneity
Dangelmajer et al 2017[243]	Y	Y	Y	CD	N	Y	N	NA
Smith et al 2016 + 2015[214, 244]	y	Y	Y	Y	N	Y	N	N
Samitier et al 2015[245]	Y	Y	Y	N	Y	Y	N	N
Rosso et al 2015[246]	Y	Y	Y	Y	Y	Y	N	N
ELAttar et al 2011[247]	Y	Y	Y	CD	Y	Y	N	N
Lee et al 2017[248]	Y[a]	y	y	Y	Y	Y	N	Y
Barber-Westin 2017[249]	Y	Y	Y	CD	Y	Y	N	NA
Bin et al 2017[250]	Y	Y	Y	Y	Y	Y	N (not possible)	Y
Jauregui et al 2017[251]	Y	Y	Y	N	N	Y	N	N
Lee et al 2017[252]	Y	Y	Y	CD	Y	Y	N	NA

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported

1. Is the review based on a focused question that is adequately formulated and described?
2. Were eligibility criteria for included and excluded studies predefined and specified?
3. Did the literature search strategy use a comprehensive, systematic approach?
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?
5. Was the quality of each included study rated?
6. Were the included studies listed along with important characteristics and results of each study?
7. Was publication bias assessed?
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)

[a]question was to assess differences between MAT in isolation versus MAT in combination with other procedures.

Table 33: Results and conclusions of reviews of MAT

Results	Conclusions
Dangelmajer et al 2017 [243] Aim to compare meniscal transplants and scaffolds	
Meniscal Allograft Transplantation. 15 articles. Follow-up range 24.9 months – 15 years Overall failure rate ranged from 0% to 33.3% (average 18.7%) Overall reported operation rate ranged from 0 – 45.3% (average 31.3%). In one study 58% reported no increase in osteoarthritis, 42% slight to moderate increase (follow-up between 5-15 years). Meniscal scaffold: 7 articles Follow-up 12 months – 11 years Average failure rate of 5.6% (ranged from 0% to 17.3%) Average reoperation rate was 6.9% (ranged from 4.2% to 9.5%).	The authors concluded that the limited number of mainly short-term scaffold studies made comparison difficult.
Smith et al 2016 + 2015 [244] [214] Aim to assess meniscal allograft transplantation in symptomatic meniscal deficient knees	
In 35 studies, with mean follow-up of 5.1 years (range 1-20 years): Lysholm scores improved from 55.7 to 81.3 IKDC scores from 47 to 70 Tegner activity scores from 3.1 to 4.7 Mean failure rate was 10.9 % at 4.8 years Mean complication rate was 13.6 % at 4.7 years. Kellgren and Lawrence scores, 3 studies: no change in one study (8.8 years follow-up); no change in 28 and 1 grade worsening in 8 patients in one study (2.6 years follow-up); 5 with no change and 5 with progression at 3.3 years follow-up in one study. IKDC radiological scores, 2 studies: minimal changes at 2.8 years follow-up in one, 1 grade worsening in 1 of 8 in one (at 8.5 years follow-up). Osteoarthritis progression: 1 study, no change in 32/34 patients at 2 years, at 10 years 15 had mild change and 5 moderate or severe progression.	2015 review: From observational studies, MAT appears to be an effective intervention in patients with a symptomatic meniscal deficient knee. Ideally, this should be confirmed by an RCT. 2016 review: There is some evidence that MAT may reduce the progression of osteoarthritis. Good quality RCTs are required to confirm this. If confirmed, there may be a role for prophylactic MAT in selected patients.

Samitier et al 2015 (2 publications, part 1 not relevant but includes some methodology, Part 2 reviewed here) [245] Aim to review optimal timing for transplantation, outcomes, return to competition, associated procedures, and prevention of osteoarthritis (part 2).	
All studies included in this review were in the more recently published reviews (above) and therefore no results have been extracted.	The authors conclude that; • MAT relieves symptoms, restores function and improves quality of life • In three small medium term studies, about 80% of patients return to sport at same level • Overall failure rate (defined as need for KR) ranged from 10-29% at long-term follow-up There is insufficient evidence to justify MAT at the time of meniscectomy, or that it is chondroprotective.
Rosso et al 2015 [246] Aim to assess the quality of the published studies on MAT; the indications ; the methods used for preservation, sizing, and fixation of the allograft; and the clinical and radiographic outcomes of this procedure and its role in preventing osteoarthritis (knees)	
The weighted average Lysholm score increased from 55.5 (2.1) preoperatively to 82.7 (2.7) at the last follow-up (varied across studies). The weighted average overall VAS score for pain decreased from 6.4 (0.4) to 2.4 (0.4) at the last follow-up (varied across studies) States some authors described a worsening of the results over time. Weighted average of overall satisfaction was 81.6% (3.8), 14 studies Slightly shorter survival for medial MAT compared with lateral MAT (2 studies) No difference in clinical outcome of survivorship between isolated MAT and MAT combined with other procedures (no data, 13 studies). Weighted average of complications: 10.6% (of complications: common tear 59.6%; synovitis or effusion 30.7%; superficial infections 6.25%; reduction in movement 2.8%; deep infection 0.6%) Weighted failure rate 8.7% (11 studies) Survival time was 9.9 – 11.6 years (2 studies); survival rate was 52.5% at 16 years in one study.	MAT provides good symptomatic results at short-term and midterm follow-up, with improvement in knee function. Complication and failure rates are acceptable. Chondroprotective remains unproven.
ELAttar et al 2011 [247]	

Mean follow-up 4.6 years (range 8 months – 20 years); 44 studies. Average Lysholm score 44 at baseline; 77 at last follow-up. Average Tenger activity score 3 at baseline; 5 at last follow-up. Overall pain VAS at baseline 48mm, at last follow-up 17mm. IKDC 84% normal or nearly normal at last follow-up 89% participants were satisfied with their outcome at last follow-up. Average original Coleman scores 45.9 ± 8.4 (range 25–59). Average modified Coleman scores 43.7 ± 9.1 (range 24–62). Failure ((sub)total destruction/removal of the graft with or without conversion to arthroplasty) rate per trial, 10.6% Complication rate overall mean, 21.3% (128 complications reported).	Studies consistently report good relief of symptoms and return to previous activities, with acceptable complication and failure rates. MAT can be considered as safe and effective for the treatment of post-meniscectomy symptoms in selected patients.
Lee et al 2017 [248] Aim to evaluate whether there is a difference in clinical outcomes between isolated MAT and MAT combined with other procedures (combined MAT).	
Mean follow-up ranged from 24.9 to 180 months; 24 studies Lysholm score, 10 studies: isolated MAT vs combined MAT mean difference -2.19 points (95% CI, –5.92, 1.55; P = 0.25; I^2 28%) Tegner score, 6 studies: isolated MAT vs combined MAT mean difference -0.16 points (95% CI -0.54, 0.22; p=0.41; I^2 4%) IKDC subjective: isolated MAT vs combined MAT mean difference -1.15 (95% CI, –5.67, 3.37; P = 0.62; I^2 34%) No pooled data for complications, reoperation or survival. Studies showed varying outcomes for survivorship and failure rates.	No significant difference found in outcomes between isolated MAT and combined MAT.
Barber-Westin 2017 [249] To determine sports activities achieved after meniscus transplantation and if associations exist between sports activity levels and transplant failure or progression of tibiofemoral osteoarthritis (OA).	
Mean follow-up 5.0 (SD 3.7 years); was less than 5 years in 69% of the studies. A quantitative analysis was not undertaken	Most people could return to low-impact athletic activities after MAT. The average short-term follow-up did not allow conclusions to be reached on the effect of

	return to high-impact activities on MAT failure rates or progression of OA.
Bin et al 2017[250] The hypothesis is that the survival rates are similar between medial and lateral MAT but that the clinical outcomes of lateral MAT are better than those of medial MAT at final follow-up.	
Mean follow-up of studies not reported but all had to be at least 5 years 5-10 year survival rates: medial, 97/113; lateral, 108/121 (4 studies, OR 0.71; 95% CI, 0.31-1.64; P = 0.42), I^2 0% >10 years survival rates: medial, 303/576; lateral, 456/805 (8 studies, OR 0.78; 95% CI, 0.52-1.17; P = 0.22), I^2 44% Lysholm score, 3 studies, MD -7.05 (95% CI -10.17, -3.94), I^2 64%, favours lateral.	Survival rates after lateral MAT were 89% at 5-10 years follow-up and 86% after medial. With longer follow-up >10 years, survival was 53% for medial and 57% for lateral MATs. Pain relief and function were better after lateral MAT than medial MAT.
Jauregui et al 2017[251] To assess the overall outcome of MAT and compare the results of different meniscal root fixation techniques	
mean follow-up of 60 (range, 25-168) months Tear rate 9% (95% CI 6.3, 12.2) Failure rate 12.6%. (95% CI 9.1, 16.6) Lysholm scores improved from 57.8 (range 35-72) pre-operatively to 81.4 (range 61-92) post-operatively; SMD 1.5 (95% CI 1.3, 1.8), P<0.001	MAT provides significant improvements in clinical outcomes patients with low failure rates. No difference was shown between soft tissue suture and bone fixation.
Lee et al 2017[252] To determine the time to and rate of the return to sports (RTS) after meniscal surgery and to compare these values among the different types of meniscal surgeries. Includes meniscectomy, meniscal repair, and MAT.	
Mean follow-up not reported (reported for individual studies) No quantitative analysis of the 4 MAT studies were reported. After MAT, 67% to 85.7% of athletes returned to sports, and the time to RTS ranged from 7.6 to 16.5 months.	RTS was quicker and higher after meniscal repair than after MAT. Combining MAT with other procedures such as ACLR delayed RTS, but had no effect on the RTS rate or level of sports activity.

Table 34: Studies included in this review

Author	Intervention details	Study Design
Abat et al [253] and Gonzales-Lucena et al [254]	MAT (2 groups different fixation methods) then sub-study of suture only group	Cohort
Carter et al [255] (abstract only)	MAT	Before and after
Cole et al [256] and Abrams et al [257 258]	MAT, with subgroup having OCA	Before and after
Kim et al [259 260 261 262 263]	MAT	Retrospective before and after study
LaPrade et al [264]	MAT	Before and after
Mahmoud [265]	MAT	Prospective case series
Noyes and Barber-Westin [266]	MAT	Before and after
Noyes et al [267 268]	MAT	Before and after
Marcacci et al [269]	MAT	Before and after
McCormick et al [270]	MAT	Case series
Riboh et al [271] adolescent group	MAT	Before and after
Rue et al [272]	MAT and OA transplant or MAT and ACI	Before and after
Parkinson et al [216] Kempshall et al [217] Middleton [273] Bloch [274]	MAT, with groups according to articular cartilage condition	Case series
Saltzman et al [275 276 277]	MAT (+ Subgroup MAT+ACL)	Before and after
Stone et al [278 279 280 281]	MAT	Case series
Van Arkel et al [282 283] and Van der Wal et al [284]	MAT	Before and after study
Van Der Straeten et al [285]	MAT	Case series
Verdonk et al [286 287]	MAT	Before and after

The 12 single arm before and after studies report variables at both baseline and follow-up. Study characteristics and baseline characteristics of the participants are summarised in Table 35. The definitions of failure used in the studies differed, and included need for revision surgery (MAT or TKA), removal of graft, and persistent pain – Table 36.

Table 35: MAT studies characteristics and participant baseline characteristics

Study	Indication / inclusion criteria	Concomitant procedures	Baselines
Barcelona			
Abat et al [253] **Country:** Spain **Study design**[a]**:** Prospective cohort study **Follow-up:** 5 years (range 2.5–10) **Sample size:** 88 (only-suture 33, bony-fixation 55)	Two studies of different ways of securing MAT, sutures or bone plugs in patients with joint pain due to a previous total or subtotal meniscectomy (postmeniscectomy syndrome), 2001 to 2008. 88 patients. 2012 paper reports extrusion rates. 2013 paper reports function and radiographic appearance	39% of only-suture group, 43% of bony fixation group, including ACL reconstruction, microfracture, chondral shaving, hardware removal, arthroscopic cartilage repair with TruFit plugs.	**Age**[a] **:** 37.3 (15-51) **% male:** 64 **Location**[b]**:** 45/55
González-Lucena et al [254] **Country:** Spain **Study design**[a]**:** Before and after **Follow-up**: 78 months (range 63-96) **Sample size:** 33	This paper report the subgroup of 33 patients from the above study who did not have bone plugs. 2001-2013	39%: ACL reconstruction, microfracture, chondral shaving	**Age**[a] **:** 38.8 (21-54) **% male:** 72.7 **Location**[b]**:** 42.4 / 57.6
Carter et al [255] (abstract only) **Country:** USA **Study design**[a]**:** Before and after **Follow-up duration**: 10 years **Sample size:** 40 (41 allografts)	Inclusion criteria not reported	73%: ACL, osteotomy, ACL/osteotomy, medial lateral ligament.	**Age**[a] **:** 34.8 (19-50) **% male:** NR **Location**[b]**:** NR
Rush Centre, Chicago, USA			
Cole et al [256] **Country:** USA **Study design**[a]**:** Before and after (author design: case series) **Follow-up**: 33.5 months (range 24-57). **Sample size:** 40 (45 transplants)	Persistent symptoms after meniscectomy, relatively well-preserved articular cartilage with less than grade III changes on radiographs and at arthroscopy, normal knee alignment, and a stable joint. Joints that could be rendered stable or realigned by a concomitant procedure at the time of transplantation were also included. Minimum follow-up 24 months. 1997-2003.	47.5% osteochondral allografts, osteochondral allografts, osteochondral autografts, microfracture, osteochondritis dissecans fixations, autologous chondrocyte implantation, chondral debridement. Also ligament reconstruction and osteotomy.	**Age**[a] **:** 31 (SD 9.5) **% male:** 61.1 **Location**[b]**:** 62.5/37.5

Rue [272] **Country:** USA **Study design**[a]**:** Before and after study (author design: case series) **Follow-up**: mean 3.1 years (SD 1.2, range 1.9-5.6) MAT+ACI mean 3.4 (range 1.9-5.6) years MAT+OA mean 2.9 (range 1.9-5.0) years **Sample size:** 30 (31 procedures)	Simultaneous combined MAT and cartilage repair procedures including ACI or fresh OCA transplantation, in the same compartment, 1997 – 2004. Inclusion criteria were persistent symptoms after meniscectomy with combined articular cartilage injury, normal alignment or correction to normal alignment, and a stable ligamentous knee examination. Minimum 24 months follow-up.	ACI 16 (52%) or fresh OA transplant 15 (48%). (ACI was chosen for relatively younger patients with superficial defects especially of the patellofemoral joint. OA grafts were chosen for older patients with larger defects of the femoral condyle with associated bone loss). Also proximal tibial osteotomy, hardware removal.	**Age**[a] **:** 29.9 (13.9-47.9) **% male:** 60.0 **Location**[b]**:** 64.5/35.5 There may be some overlap with Cole 2006[256] because same centre and all operations done by single surgeon, but only 3 patients in Cole 2006 had OCA. Also with Abrams.
Abrams et al [257, 258] **Country:** USA **Study design**[a]**:** Before and After (author definition case series **Follow-up:** mean 4.4 years (range 2-11) **Sample size:** 32	Persistent symptoms after meniscectomy, an isolated ICRS grade 3 or 4 defect of the femoral condyle, normal alignment or correction to normal alignment, ligamentous stability, and minimum 2-year clinical follow-up. 2003 – 2009.	Series having combined MAT and OCA. A small percentage underwent other concomitant procedures, no further details.	**Age**[a] **:** 35.0 (10.0) **% male:** 53.1 **Location**[b]**:** 75 / 22 / both 3
Saltzman et al [275 276 277] **Study design:** retrospective analysis of prospectively collected data. Various subgroups **Follow-up:** No chondral defect (ND) 4.48 (SD 2.63) years, Full-thickness chondral defects (FTD) 3.84 (SD 2.47) years[276 276] Concomitant ACL reconstruction [275]: mean 5.7 (SD 3.2) years (range 1.7-16.5)[275] **Sample size:** 91 (of 457 operated), 22 ND, 69 FTD. Group of n=40 (of 53) with concomitant ACL reconstruction [275]	All patients who underwent medial or lateral MAT by a single surgeon 1997 – 2013 (1999 - 2014[275]. Inclusion criteria: patients with osteochondritis dissecans; isolated single lesions, multiple lesions or bipolar lesions; and minimum 2 years of follow-up.	ACL reconstruction: ND 38%, FTD 12%; cartilage procedure: ND 0%, FTD 100% (OCA70%, ACI 19%, microfracture 13%, OATS 4%, DeNovo 1%); realignment procedure ND 9%, FTD 10%) Group with concomitant MAT+ACL reconstruction, n=40 [275] (100%)	**Age**[a] **:** ND 26.8 (10.7); FTD 30.4 (10.3); subgroup 30.3 (9.6) **% male:** ND 63.6 FTD 46.4. Subgroup 53 **Location**[b]**:** ND 77.3 / 22.7; FTD 56.5 / 43.5. Subgroup[b] 83 / 17
Riboh et al [271] Adolescent subgroup **Study design:** retrospective analysis of prospectively collected data	Age ≤ 16 years at index procedure; MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment undergoing meniscectomy) for which	47% (31% ACI, 6% ACL reconstruction, 3% ACI biopsy, 3% OATS, 9% OA, 3% high tibial osteotomy)	**Age**[a]**:** 15.4 (1.04) **% male:** 28.1 **Location**[b]**:** 16 / 84

Follow-up duration: 7.2 years (SD 3.2, range 2 to 15) **Sample size**: 27 (of 32 enrolled, but 23 in results tables)	conservative treatment failed; procedure ≤ 2012; and minimum 2-year clinical follow-up		
McCormick et al [270] **Study design:** retrospective review of prospectively collected data **Follow-up duration:** 59 months (range 24-118) **Sample size**: 200 subsequent surgery 172 at final follow-up	MAT in isolation or in combination with cartilage repair or regeneration techniques and bony realignment procedures, 2003 to 2011	60% (37% cartilage procedure, 7% cartilage procedure and osteotomy, 11% ACL reconstruction, 8% osteotomy)	**Age**[a]**:** 34.3 (10.3) **% male**: 50 **Location:** 64/36/1 (medial/lateral/both)
LaPrade et al [264] **Country:** Vail Colorado, USA **Study design**[a]**:** Case series **Follow-up**: 2.5 years (range 1.8-4.0) **Sample size:** 40	Uni-compartmental knee pain and post-activity effusions after total or near-total meniscectomy in patients with closed physes. Patients either demonstrated ligamentous stability or underwent a concurrent cruciate ligament reconstruction surgery to address their instability. 2003-2006.	52.5% Revision ACL reconstruction, ACL reconstruction, hardware removal, microfracture of femoral condyle, osteoarticular allograft, distal femoral osteotomy.	**Age**[a] **:** 25 (16-42) **% male:** 67.5 **Location**[b]**:** 47.5/52.5
Mahmoud et al[265] **Country:** Brisbane, Australia Study design: consecutive series Follow-up: mean 8.6 years (SD 3.4 yrs) Sample size: 45	Patients with pain after meniscectomy, despite minimum of six months non-operative treatment (physio, knee braces, reduced activities). Exclusions: radiographic or arthroscopic evidence of bone-on-bone articulation.	42%, ACL, PCL, osteotomy, chondral repair	**Age:** 35 **%male:** 51% **Location**[b]: 66/34
Marcacci [269] **Country:** Bologna, Italy **Study design**[a]**:** Before and after (author description: case series) **Follow-up**: mean 40.4 (SD 6.90, range 36-66) months **Sample size:** 32	Patients with total or subtotal chronic meniscal injuries considered eligible for MAT: unicompartmental knee pain after total or subtotal meniscectomy (meniscus loss greater than 75%), anterior cruciate ligament deficiencies stabilized at the time of the index	31%: ligament reconstruction surgery for patients with ligamentous instability or osteotomy (details reported).	**Age**[a] **:** 35.6 (10.03) **% male:** 72 **Location**[b]**:** 50/50

	surgery, age 15-55 years, and contralateral healthy knee. 2005-2009.		
Noyes and colleagues			
Noyes et al [267] [268] **Country:** Cincinnati, USA **Study design**[a]**:** Before and after study (author description: case series) **Follow-up**: average 40 months (range 24-69). 2015 study, all 40 transplants 11.0 (range, 0.2 to 17.7) years; 18 transplants completing long-term evaluation: 13.7 (range 8.4 – 17.3) years. **Sample size:** 38 (40 transplants)	Prior meniscectomy, ≤ 50 years, clinical symptoms of pain in the tibiofemoral compartment, no radiographic evidence of advanced arthrosis, and ≥2 mm of tibiofemoral joint space on 45° weight-bearing postero-anterior radiographs. 1995 – 2000.	40% osteochondral autograft transfer; 10.5% knee ligament reconstruction; 18.4% anterior cruciate ligament reconstruction; 2.6% medial collateral ligament reconstruction; 2.6% posterior cruciate ligament reconstruction.	**Age**[a] **:** 30 (14-49) **% male:** 52.6 **Location**[b]**:** 47.4/47.4/ both 5.3
Noyes and Barber-Westin [266] **Country:** USA **Study design**[a]**:** Case series **Follow-up**: unclear for total, appears to be up to 17.3 years (was 13.1 (3.1) years for those failing not requiring surgery) for survival. For functional outcomes was 11.2 (3.2) years (but 10 [2.6] years for those who required later reoperations and 13.3 [2.9] years for those not requiring further surgery). **Sample size:** 69 (72 transplants)	Prior meniscectomy, <50 years, pain in the involved compartment, ≥2 mm of retained tibiofemoral joint space on 45° weight bearing posteroanterior (PA) radiographs, no or only minimal bone exposure on tibiofemoral surfaces, normal axial alignment. 1995-2005	39% of knees concurrent procedures (osteochondral autograft transfers; knee ligament reconstructions; revision knee ligament reconstructions).	**Age**[a] **:** 30 (14-49) **% male:** 47.8 **Location**[b]**:** 56.9/43.1
Spalding and colleagues, Coventry, UK			
Parkinson et al [216]**, Kempshall et al** [217] **Middleton** [273] **Bloch** [274] **Country:** Coventry, UK **Study design**[a]**:** Prospective cohort **Follow-up**: 3 (range 1-10) years **Sample size:** 125	<50 years, experiencing pain, history of total or subtotal meniscectomy in the same compartment of the knee. 2005 – 2014. Divided into three groups according to state of articular cartilage.	55.2% had associated procedures Kempshall Group A 35%, Group B (bare bones) 79.5%, including osteotomy, revision ACL, meniscal repair, matrix ACI, microfracture, Trufit plug.	**Age**[a] **:** 31.0 (8-49) **% male:** 68.8 **Location**[b]**:** 20/80

	The Middleton article reports results in 23 children and adolescents, age range 8 to 18.		
The Stone Group, San Francisco			
Stone et al [279] **Country:** USA **Study design**[a]**:** Case series **Follow-up**: 5.8 years (2 mo to 12.3 yrs). **Sample size:** 115 (119 MATs)	Aim: to determine whether MAT will survive in an osteoarthitic knee (Outerbridge grades III and IV). 1997-1999 45 patients. Mean age 48, range 14 to 69 years.	All had other procedures to smooth rough articular cartilage (chondroplasty) and most had more than one. Failure was removal of MAT or joint replacement.	89.4% MAT survival with mean failure time at 4.4 years. Highly significant improvements in pain and, activity. So OA is not a contraindication to MAT.
Stone et al [278]	119 MATs with simultaneous articular cartilage repair. Pain in the knee due to irreparable damage to the meniscus, or loss of > 50% of the meniscus. Outerbridge grade III or IV changes in the respective compartment. 1997-2008 Age[a] : 46.9 (14.1-73.2). Almost half over 50. 70% male Location[b]: 71.4/28.6	92% had at least one additional procedure, with a range of one to nine. These included articular cartilage repair by microfracture 69) and articular cartilage paste grafting (67), medial opening tibial osteotomy (15) and ACL reconstruction (17).	Failure in 25 = removal of MAT (7) or KR (18, TKR 10, UKR 8). Revision with new MAT not counted as failure.
Stone et al [280 281] **Country:** USA **Study design:** Case series (retrospective review of prospectively collected data) **Follow-up duration**: mean 8.6 (SD 4.2, range 2-15) years **Sample size:** 49 (76 in the initial study group [68 in earlier abstract] of 159 in the total MAT population)	Those receiving MAT, previous participation in competitive sports who had a pre-injury Tegner level of ≥8, a desire to participate in sports and Outerbridge (OB) Grade III or Grade IV changes. Subset of 49 patients having MAT on background of moderate to severe articular cartilage damage (OB grade IV in 41, with aim to assess return to active sports. Mean follow-up 8.6 years, minimum 2 years after MAT	12.2% medial opening wedge osteotomy (prior to 2003); 69.4% articular cartilage repair (microfracture alone, articular cartilage paste graft alone, or combined); 8.2% ACL reconstruction. 22.4% had cartilage repair 6 weeks prior to MAT.	**Age (range):** 45.3 (14.1 to 73.2) **% male:** 73.5 **Location**[b]**:** 73.5 / 24.5 74% returned to sport with improvements in pain and function, but 11 (22%) of MATs failed at mean of 5.2 years
Bin and colleagues, South Korea			
Kim et al 2017 and Lee et al [259 260 261 262 263]	Knees that underwent MAT in a single hospital (1996 – 2009) and were followed up for a minimum of 2 years. Indications: previous	At time of MAT or a separate operation: surgical treatment of ACL tears (20% knees); osteochondritis	**Age (median range):** 33.1 (16-57) **% male:** 72.6

Study design retrospective before and after study (author description case series) **Follow-up:** mean 49.4 (range 24-164) months **Sample size:** 106 (110 knees)	subtotal or total meniscectomy followed by persistent swelling and pain in the involved compartment during activities of daily living	dissecans (3.6% knees); ACL tear with posterolateral corner injury (0.9% knees) and PCL tear (0.9% knees).	**Location[b]:** 74.5 / 25.5
Van Arkel et al and van der Wal et al[282] [283] [284] **Country:** The Netherlands **Study design:** Before and After **Follow-up duration:** 13.8 (SD2.8) years (2009); 60 months (4 to 126) (2002) **Sample size:** 57 at 60 months; 46 at 13.8 years	Patients younger than 55 years with disabling compartmental osteoarthritis after meniscectomy in first 23, then changed to younger than 45 years with stable normally aligned knees but disabling compartmental osteoarthritis after meniscectomy, 1989 - 1999	3.5% ACL repair, no further details	**Age[a]:** 39.4 (6.9) **% male:** 70.2 **Location:** 29.8/59.6/10.5 (medial/lateral/both)
Van Der Straeten et al[285] **Country:** Belgium **Study design:** Case series (Retrospective review of prospectively collected data). **Follow-up duration:** mean 6.8 (range 0.2-24.3) years **Sample size**: 265 (of 313 enrolled)	<60 years, moderate to severe knee symptoms (pain, swelling, instability) shortly after total meniscectomy or after a failed meniscus replacement with an artificial polyurethane meniscus or a collagen meniscal implant. In 6 the MAT was a replacement after failure. 1989 – 2013	35.8% including microfracture, osteochondral autograft transfer system, high tibial osteotomy and ACL reconstruction.	**Age (range):** 33.3 (15-57) **% male:** 60 **Location[b]:** 36 / 64 N=313 allografts
Verdonk et al 2005 [286] [287] **Country:** Belgium **Study design:** before and after (retrospective analysis of prospectively collected data) **Follow-up duration:** mean 7.2 (SD 3.6) years (range 0.5 to 14.5) **Sample size:** 100	Moderate-to-severe pain in a younger patient (<50 years) who had undergone a previous total meniscectomy, was not old enough to be considered for a knee joint, moderate-to-severe pain. 1989-2001.	49% of medial allografts and 20% of lateral allografts, High tibial osteotomy 15%, femoral varus osteotomy 2%, ACL reconstruction 3%, osteochondral plug transfer 4%, microfracture 3%.	**Age[a]:** 35.0 (6.7) **% male:** 72.9 **Location:** 38.5/59/2 (medial/lateral/both)

[a]mean (range) unless stated otherwise; [b] % medial / lateral

Table 36: Definitions of failure after MAT

Study	Definition
Abat et al and González-Lucena et al [253] [254]	Complete removal of allograft
Cole et al [256]	Required conversion to a unicompartmental or total knee arthroplasty
Kempshall et al [217] [216] and Parkinson et al	Complete removal, revision or conversion to joint replacement
Kim et al [260] [259] [261]	Poor overall results on MRI, arthroscopy or modified Lysholm; or non-satisfactory overall results
Marcacci et al [269]	Developed lack of flexion and underwent arthroscopic arthrolysis or symptomatic posterior horn flap lesion of the graft with no history of trauma, or underwent arthroscopic selective meniscectomy and debridement
McCormick [270]	Revision MAT or KA
Noyes et al [267]	2004: Persistent pain or mechanical damage (a detached or torn allograft)
Noyes and Barber-Westin [266]	Results reported for: 1) reoperations related to failure of transplant (transplant removal or revision, total knee arthroplasty, unicompartmental knee arthroplasty, or osteotomy) 2) MRI failure (grade 3 signal intensity or extrusion >50% of the meniscus transplant width) and/or radiograph failure (or loss of joint space in the involved tibiofemoral compartment on 45 degree weightbearing PA radiographs (IKDC grade D) with no reoperation required.
Riboh et al 2016 [271]	Not reported (revision MAT was an outcome however)
Rue et al [272]	Revision of either the MAT or cartilage repair procedure or arthroscopic confirmation of MAT or cartilage repair failure
Saltzman et al [275] [276] [277]	Additional ACL reconstruction procedure, revision MAT, or conversion to unicompartmental or tricompartmental total knee arthroplasty (reported separately except in the subgroup paper)
Stone et al [278] [279]	Removal of the allograft without revision, or progression to a total or unicompartmental knee replacement (removal and revision with implantation of a new meniscal allograft was counted in subsequent surgical procedures).
Stone et al [278] [281]	Progression to knee arthroplasty, surgical removal of the MAT without revision, pain greater than pre-operatively, or constant moderate pain with no relief from non-operative treatment.

Van Arkel et al and van der Wal et al [282] [283] [284]	Persistent pain, unsuccessful KASS, poor Lysholm score, detached allograft (2002); complete resection of the graft, with or without placement of unicompartmental knee arthroplasty or TKA(2009)
Van Der Straeten et al [285]	Removal of allograft including during conversion to TKA or UKA
Verdonk et al [286] [287]	Moderate or severe occasional or persistent pain (HSS pain subscore <30) or poor knee function (HSS function score <80), or conversion to total or unicompartmental knee arthroplasty

ACL: Anterior Cruciate Ligament; HSS: Hospital for Special Surgery; KASS: Knee Assessment Scoring System; TKA: total knee arthroplasty; UKA: unicompartmental knee arthroplasty

Mainly because of the observational design and sometimes lack of details of methods, the quality of these non-randomised studies was mostly graded fair, with only two studies [269] [281] rated as good, because they reported intervention and results more clearly, and two studies rated as poor due to insufficient reporting of selection criteria, high loss to follow-up and lack of blinding of outcome assessors [264] [255] and lack of statistical comparison before and after the intervention [255]. Interpretation of some studies was complicated by other procedures, for example in one study by Saltzman et al [276] all patients in the full thickness defect arm had cartilage repair procedures, mainly osteochondral allograft. Saltzman et al [277] also reported outcomes for 40 patients undergoing concomitant MAT and anterior cruciate ligament reconstruction. Where reported, around 20-60% of people underwent concomitant procedures, as noted in Table 35.

Cohort size in the included studies ranged from 30 to 313, with a total of 1731 people undergoing at least one MAT. Twelve of the studies were conducted in the USA. Average follow-up in the studies ranged from 2.5 years to 17.3 years, although there was a large variation in the ranges. The key indications for MAT or study inclusion criteria are given in Table 33, but the usual indication was persistent symptoms after meniscectomy.

Some studies (such as Cole et al 2006 [256] included only patients with relatively well-preserved articular cartilage, or well-aligned knees [254], but others included people with more evidence of advanced OA (Saltzman 2017 [276], Stone 2015 [281] partly to assess survival of MAT in the knees with OA. Marcacci et al [269] required the other knee to be healthy. Rue et al [272] included people undergoing simultaneous combined MAT and cartilage repair procedures including autologous chondrocyte implantation (ACI) or fresh osteochondral allograft (OCA) transplantation, in the same compartment. Abrams et al [257] [258] included people undergoing combined MAT and OCA transplant. A proportion of the people in the remaining studies underwent a variety of concomitant procedures (around 31%-73%), these are summarised in Table 35. Mean age mostly ranged from 25 to 45 years, although in the study by Stone et al [278] the mean age was 47 years. The studies by Riboh et al [271] and Middleton et al [273] included only children and adolescents, age ranges 13-16 years and 8-18 years. The proportion of men in the studies ranged from 48-80%, with the majority of studies having at least 60% men. The Riboh and Middleton studies in the under 18s had more girls than boys.

Failure and survival

Graft failure, as shown in Table 37, ranged from 3.6% in the bony-fixation subgroup of Abat et al [253] (success defined as patient satisfaction at 5 years follow-up) to 29% in the studies by Van der Wal (13.8 years of follow-up). [288]. Kempshall et al [217] found that when failure occurred it was early, potentially indicating a problem with healing or integration of the graft, and reported a mean time to failure of 1.12 years (range 0.47–1.85; SD 0.55). Time to failure ranged from mean 5.2 years in the study by Stone et al[281] to 10.3 years in the one by Van der Wal [284] These rates reflect the baseline state of the knees, with the patients in the Stone et al study having significant OA.

Table 37: Failure rates in MAT studies

Study	Number of MATs	Mean FU(range) years	Defn failure	Proportion failed
Abat et al [253] González-Lucena et al [254]	88 Suture fixation 33 Bony fixation 55	5 yrs (2.5 to 10)	Removal of graft	Suture only 9% Bone fixation 3.6%
Cole et al [256]	40	2.8 yrs (2-4.8)	Conversion to KA	7.5%
Kim et al [261]	110	4.1 yrs (2-13.7)	Poor clinical results Failure (resection, TKA, poor Lysholm	10.9% 2% 10 year, 7% 15 years
Marcacci et al [269]	32	3.4 yrs (3-5.5)	Debridement, meniscectomy or poor result	6.3%
Mahmoud et al [265]	45	8.6 yrs (SD3.4)	Removal of MAT or KA	OCS 0-2 no failures OCS 3-4 26%
McCormick et al [270]	200	4.9 yrs (2 – 9.8)	Revision MAT or TKA	4.7% 1.5% conversion to KR
Noyes et al [267]	40	3.3 yrs (2.0-5.8)		7.9%
Noyes and Barber-Westin [266]	58	17.3 yrs	Persistent pain or detached or torn allograft	15.3%
Parkinson et al [216], Kempshall et al [217]	124	3 yrs (1 -10)	Graft removal, revision MAT or KA	10.5% overall At 2 years, survival 98% if chondral surface good, 78% if chondral surface bare
Riboh et al [271]	32	7.2 yrs (2-15)	Not reported (but revision MAT was an outcome	22%
Rue et al [272]	31	3.1 years	Revision or removal	6%
Saltzman et al [276]	ND 22 FTD 69 MAT+ACL 40	ND 4.5 yrs FTD 2.5 yrs MAT+ACL 5.7 yrs	Revision MAT or KA	ND 15% FTD 16.2% MAT+ACL 20%
Stone et al [278]	119	5.8 yrs (0.2-12.3)	Removal of the allograft without revision, removal and new MAT, or KA	20.1%
Stone et al [281]	49	8.6 yrs (2-15)	KA, removal of MAT, pain greater than pre-operatively, or constant moderate pain	22.4%

			with no relief from non-operative treatment.	
Van der Wal et al {#128	63	13.8 yrs (SD2.8)	Persistent pain, unsuccessful KASS, poor Lysholm score, detached allograft (2002); removal of MAT,UKA or TKA(2009)	29%
Van der Straeten et al [285]	329	6.8 (0.2-24.3)	Removal of MAT, KA	27.4% 19% to KR
Verdonk et al [286]	100	7.2 yrs (0.5 – 14.5)	HSS pain subscore <30, HSS function score <80,KR	Medial 28%, lateral 16%

HSS: Hospital for Special Surgery; KASS: Knee Assessment Scoring System; TKA: total knee arthroplasty; UKA: unicompartmental knee arthroplasty. ND – no chondral defect. FTD full thickness chondral defect

The Kempshall and Bloch reports [217 274] show that MAT gives better results in terms of failure rates, if done before the articular cartilage is advanced to the stage of bare bone, with 2-year survival 98% amongst those with articular cartilage in good condition, versus 78% in those with poor condition, but even then it was beneficial with similar absolute increases in clinical scores, though from different baselines. The more advanced group had more concomitant procedures (about 80% compared to 35% in the good cartilage group) with the difference mainly in microfracture.

From the same group, Parkinson et al [216] reported the results of a series of 125 MATs over a 10-year period, with median follow-up 3 years but range 1-10 years. Those with ICRS grade 3b changes (full thickness articular cartilage loss on either femoral condyle or tibial plateau or both) had much higher failure rates 5 years after MAT. The Kaplan-Meier survival curves show most failures (defined as a need for removal or revision of the MAT or knee replacement) occurred in the first 4-5 years. Survival was better with lateral than with medial allografts. The mean age at meniscectomy was 24 and at MAT 31 years (range 8 to 49 years). However, even in the worst group with bare bone on both femur and tibia, the 5 year MAT survival was 62%.

The proportions having reoperations, including revision MAT, debridement or removal of the allograft, varied amongst studies, partly because of duration of follow-up. In their study of 329 MAT implants, Van der Straeten et al [285] reported that 27% of allografts were removed after a mean time in situ of 8.5 years. In the study of 200 patients by McCormick et al [270], 32% had subsequent surgery by a mean follow-up six years, with mean time to re-operation 21 (range 2-107) months. Abat et al [253] and González-Lucena et al [254] reported that 21.4% and 7.3% of the suture-only (by 6.5 years) and bony-fixation groups (by 5 years), respectively, underwent revision surgery involving refixation or removal of the allograft. Carter et al [255] found 17.5% had had partial meniscectomy by 10 years of follow-up. Noyes and Barber-Westin [266] reported that during 15 years follow-up of 69 patients, half required reoperation relating to failure of the transplant (removal 15, revised 6, TKA 10, osteotomy 2, unicompartmental knee arthroplasty (UKR) 4). In the study in adolescents by Riboh and colleagues [271] only two of 32 MATs required meniscal re-operation after mean follow-up of 7 years. In the study of children and adolescents by Middleton et al [273], only two required further meniscal surgery (one partial meniscectomy, one resuture of partial tear).

Repeat MATs were performed in 2% of cases by van der Straeten et al [285], in 6% by McCormick et al [270], in 10% (4 of 40 MATs) by Noyes and Barber-Westin [266], in 10% (5 of 49) by Stone et al [281], and 12% in the study by Saltzman et al [276]. Three studies reported no repeat MATs [253, 255 271].

Conversions to TKA or UKA varied with duration of follow-up, being reported in 3% of cases in the 2017 Saltzman study [276] after a mean follow-up of 4 years, 6% in the study by McCormick et al [270] by 6 years, 7% in the study by Cole et al [256] with mean follow-up 33 months, 19% in the Van Der Straeten study [285] at a mean of 11.5 years, and 25% by 15 years in the study by Noyes and Barber-Westin 2016. [266]

Nine studies reported Kaplan-Meier survival analysis at various time points as shown in Table 38. Five year survival rates were very good but varied amongst group according to the state of chondral surfaces at baseline, as shown in the group with full thickness chondral loss on both condyles in the study by Parkinson et al. [216]. Ten-year survival ranged from 45% in the “worst case” results from Noyes and Barber-Westin [266] to over 90% in the studies by Kim et al 2012 [261] and McCormick [270], but most studies reported survival in the 60% to 75% range. However as Noyes and Barber-Westin [266] report, some of the failures in their worst case scenario were found only on radiographic or MRI imaging, in patients with no symptoms.

Table 38: Long-term survival of MAT

Study	Survival at 5 –year time periods			
	5 years	10 years	15 years	20 yrs
Kim [261] subgroup with ≥8 years follow-up		98%	93%	
Parkinson [216] Group 1 Group 2 Group 3	 97% 82% 62%			
Mahmoud [265]	92% (from graph	75% (from graph)		
McCormick 2014 [270]	95% [a]	93% (from graph)		
Noyes and Barber-Westin [266] Worst case Clinical failures	 77% 84%	 45% 64%	 19% 50%	
Saltzman MAT+ ACL [277]	84%	45%		
Van der Wal [284]	95% (from graph)	67% (76% lateral, 56% medial)	53%	
Van der Straeten [285]	80%	75%	50%	15% at 24 years
Verdonk et al [286] Lateral MATs (n=61) Medial MATs (n= 39) Medial MATs with high tibial osteotomy (n= 13)	 90% 86% 100%	 70% 74% 83%	At 14 years 70% 53% 83%	

Noyes and Barber-Westin worst case includes some patients with no symptoms related to the transplant but who have MRI grade-3 signal intensity, major extrusion or a tear , signs of a meniscal tear on clinical examination; or radiographic complete loss of joint space. Clinical failures include transplant removal or revision, total or unicompartmental knee replacement, osteotomy, or pain with daily activities

Figures for Stone and Van der Straeten 5, 10 and 15 years, taken from KM graphs and are approximate

Parkinson et al. Baseline data. Group 1 intact articular cartilage or partial thickness loss. Group 2 full thickness loss on one condyle. Group 3 full thickness loss on both condyles.

Kim defined failure defined as resection of graft, conversion to THA, or Lysholm score <45 or less than before MAT.

[a] McCormick – but 32% had subsequent surgery usually debridement.

Fifteen-year survival ranged from 19 to 93%, but the 19% was in the Noyes and Barber-Westin worst case scenario, whereas the clinical survival rate was 50%[266]. Most studies reported about half of the MATs surviving at 15 years.

Van der Straeten et al [285] reported 15.1% survival at 24 years, with a mean allograft survival time of 15.2 years.

So for economic analysis, it might be reasonable to assume around 20% have repeat surgery in the short-term but, based on the 15-year follow-up in the study by Noyes and Barber-Westin, around half in the longer term, but that clinical success rate at 15 years seems good compared to the natural history in untreated meniscectomised patients.

Progression of osteoarthritis

Carter et al [255] reported that at 2 years, 5.9% had mild progression, by 10 years 44.1% had mild progression, 14.7% had moderate to advanced progression, and 41.2% had no change. Unfortunately, this study was reported only as an abstract. It reports that plain radiographs were obtained at 2 and 10 years, but not whether progression was based only on radiography. Some X-ray progression is asymptomatic, as reported by Noyes and Barber-Westin [266]. It might be reasonable to assume that the 14.7% would need TKA but that the 44% with mild OA would get by with analgesics. The 14.7% is similar to the results of the 15 year follow-up by Noyes and Barber-Westin.

Verdonk et al [289] reviewed 17 studies of radiological progression. Most studies were short-term (under 5 years) and showed no significant progress but the four studies with longer follow-up (10 years or longer) reported joint space narrowing in 48%, 67%, 75% and all patients.

The systematic review by Smith et al [214] concluded that there was some evidence that MAT reduces progression of OA, but most studies had short durations of follow-up, the longest being a study by Verdonk et al [287] with 12 years follow-up, though in that study 11 of the 41 patients also had tibial osteotomy.

In their study of 313 participants, van der Straeten et al [285] reported progression of osteoarthritis as measured by the KL scale. At a mean of 6.8 years 40% of participants had no progression, 35% progressed more than grade 1, 20% more than two grades and 5% more than three grades.

Ahn et al [224] reported the result of 69 MATs carried out by a single surgeon from 2005 to 2012. OA was defined by KL grade changes. Patients having any concomitant surgery were excluded, as were patients with OA worse than KL grade 2. Most (about 80%) had KL 0 or 1. At 3-year follow-up, progression of OA was seen in 31 patients at average follow-up 5.5 years, but not in 38, mean FU 4 years. They noted that progression was more frequent after medial meniscectomy than lateral, with medial: lateral odds ratio 3.4 (95% CI 1.2 – 9.3, p = 0.018). However, there were no differences in Lysholm or Tegner scores between the groups. Ahn et al[224] concluded that it was possible that MAT reduced the risk of OA but that RCTs were necessary.

Functional outcomes

Table 39 shows results for functional outcomes. Nine studies reported Lysholm scores, all showing good results, with most reporting improvements of over 20 points. Eight reported International Knee Documentation Committee (IKDC) scores, with improvements ranging from 14.8 to 29.8, with most studies reporting gains of over 20 points. Five studies showed improvements in Tegner scores.

Table 39: Functional outcomes after MAT

Study (and number of initial patients)	Baseline value (SD)	Endpoint value (SD)	Change (Note 1)	P value
	Lysholm			
Abat et al [253]	65.4 (11.6)	88.6 (7.2)	23.1 (NR)	<0.001
Carter et al [255] n= 40	47 (32-68)	71 (38-95)	24 (NR)	
Cole et al [256] n=36	52.4 (20.26)	71.6 (19.7)	19.2 (NR)	p<0.05
Kim et al[261] Modified Lysholm (N= 110)	73.2 (10.6)	89.4 (13.2)	16.2 (NR)	p<0.001
Marcacci et al [269] n=32	59.8 (18.3)	84.8 (14.4)	25 (NR)	p<0.0001
Saltzman et al [276] ND (n=22) FTD (69)	 41.5 (22.3) 43.4 (17.4)	 NR NR	 14.8 (14.4)[a] 21.1 (19.8) [a]	 NR NR
Saltzman et al [277] MAT + ACL (40)	44 (16)	67 (22)	23 (NR)	<0.01
Riboh et al [271]	43.80 (20.37), n=30	58.52 (17.92), n=23	14.4 (NR)	p=0.03
Rue et al [272] n=28	48.7 (16.4)	74.0 (17.7)	25.3 (NR)	p<0.001
Van der Wal et al [284] n=49	36.36 (18)	61.06 (20)	24.7 (NR)	P=0.001
	IKDC			
	Baseline value (SD or 95% CI)	Endpoint value (SD or 95% CI)	Change (SD)	P value
Carter et al [255] n=40	50.6 (32.2-68.9)	70.1 (39.1-93.1)	19.5 (NR)	
LaPrade et al [264] n=40	54.5	72.0 (n=34)	17.5 (NR)	p<0.001
Marcacci et al [269] n=32	47.4 (20.6)	77.2 (15.6)	29.8 (NR)	p<0.0001
Rue et al[272] n=28	38.7 (12.7)	66.9 (17.2)	28.2 (NR)	p<0.001
Saltzman et al [276]				
ND, n=22	41.5 (22.3)	NR	14.8 (14.4)	NR
FTD, n= 69	43.4 (17.4)	NR	21.1 (19.8)	NR
Saltzman [275] Concomitant MAT+ACL n=40	44 (16)	67 (22)	23 (NR)	p<0.01
Riboh et al [271] n=32 (Subset of Cole study)	40.2(19) n=27	65.0 (17.7) n=23	24.8 (NR)	p<0.0001
Stone et al [278] n=115	45 (n=66)	70 (n=15)	25 (NR)	p<0.001

Stone et al [281] n=49	Median[b] 48	75	27 (NR)	p=0.001
	Tegner			
	Baseline	Endpoint	P value	
Cole et al [256]	5.0 (2.8)	6.5 (2.7)	P<0.05	
González-Lucena et al [254]	3.1 (2.1)	5.5 (2.1)	p <0.001	
Marcacci et al [269]	3 (IQR 3.5)	5 (IQR3-6)	P=0.012	
Rue et al [272]	5.0 (3.3)	6.7 (2.3)	P = 0.001	
Stone et al [281] (medians)	2.8	5.2	P = 0.32	

Note. Where papers have not reported changes, these have been calculated but SDs, SEs and CIs are not available. NR = not reported by study authors.

The studies by Noyes et al [267] and Noyes and Barber-Westin [266], using the Cincinnati Knee Rating System (CKRS), reported statistically significant improvements in pain, swelling, perception, walking and stairs, but not in the knee giving way. LaPrade et al [264] found a highly statistically significant improvement in the overall CKRS, from 55 to 73.

Five studies[256] [217] [271] [272] [275] reported Knee injury and Osteoarthritis Outcome Score (KOOS), and found statistically significant improvements in all subscales, except for the pain subscale in one small study in an adolescent population[271] Another only reported the endpoint values and is of limited value [284]. In the study by Saltzmann et al [275] the improvement exceeded the minimally clinically important differences on the symptoms and quality of life subscales in two subgroups that reported this, and in pain and sport in the full-thickness chondral defects subgroup.

Cole et al [256] and Rue et al [272] also reported statistically significant differences in the Noyes symptom and sports activity scores.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used in three studies [271] [277] [278] with some significant improvements in the function and total scores (Supplementary file Table 6). Stone et al [278] [279] found a significant ($p < 0.001$) improvement in overall score and pain after 10 years.

Kempshall et al [217] reported outcomes by baseline articular cartilage state (Table 40) showing that end results were poorer in patients with more severe baseline articular cartilage damage than in those with good chondral surface states., but they started with poorer scores and the actual improvements were of similar magnitude, for example with improvements in Lysholm scores of 21.6 in the good baseline group (58.6 to 80.2) and 24 in the poor group (47.3 to 71.4), when grafts survived.

Mahmoud et al [265] also noted greater improvements in Lysholm and IKDC scores in those with more advanced chondral damage at baseline (Table 38).

Table 40: Functional outcomes by baseline joint state.

Kempshall et al [217]		
Lysholm Knee score at final endpoint, mean (SD)[a]		
	Chondral surface good, n=60	Chondral surface bare n= 39
Baseline value Endpoint value P-value	58.6 (4.8) 80.2 (5.0) p<0.001	47.3 (6.6) 71.4 (7.8) p<0.001
IKDC score at final endpoint, mean (SD)		
Baseline value Endpoint value P-value	43.13 (4.1) 68.8 (5.5) p<0.001	37.3 (5.3) 58.7 (8.2) p<0.001
Tegner score at final endpoint, median (range)		
Baseline value Endpoint value P-value	2 (0–7) 4 (1–10) p<0.05	2 (0–9) 4 (1–9) p<0.05
Mahmoud et al [265]	OCS 0-2	OCS 3-4
Lysholm knee score		
Change from baseline	+ 21.3	+24.5
P value	P= 0.013	P <0.001
IKDC		
Change from baseline	10.8	21.5
P value	P = 0.241	P =0.001
Tegner		
Change from baseline	1.73	0.53
P value	P=0.015	P = 0.47

OCS – Outerbridge Cartilage Score

Lee et al [290]also report benefit from MAT in patients with advanced bipolar chondral lesions, with no difference in post-operative Lysholm scores between those with baseline ICRS scores $\leq$ 2 and those with more advanced chondral damage (baseline data not provided for subgroups). Clinical failure rates were not significantly different (low grade damage 7%, high grade 5%, but there were small numbers and wide CIs) but graft survival rates by MRI or follow-up arthroscopy showed a much lower survival rate in the group with high grade lesions on both sides at baseline (62%) compared to those with low grade lesions (94%).

One study each reported the Knee Society Score (KSS) [261] and Hospital for Special Surgery (HSS) score [286] and reported statistically significant improvements.

Quality of life

Six studies [257] [256] [269] [271] [272] [275] (Table 41) reported QoL using Short-From 36 (SF36) or the shorter subset, SF-12. One [275] found no significant differences Cole et al [256] and Riboh et al [271] found improvements in the physical but not mental scores, as did Abrams et al [257] in a group having combined MAT and osteochondral allografts. Rue et al [272] found a statistically significant improvement in the physical SF-12 only in the subgroup that had combined MAT and autologous chondrocyte implantation. Both physical and mental components were significantly improved in the study by Marcacci et al [269] which was rated highly, based on appropriate selection of participants, sample size calculation, blinding of outcome assessors and no losses to follow-up.

Table 41: Quality of life in MAT studies

Outcomes, mean (SD)	Kempshall et al[a][217]		Cole et al [256]	Marcacci [269]	Rue [272]	Abrams et al [258]	Riboh [271]
	Chondral surface good n=60	**Chondral surface bare n=39**	**n=36**	**n=32**	**n=28**	**n=32**	
KOOS QoL Baseline value Endpoint value P-value	 28.9 (5.0) 52.7 (7.1) p<0.001	 22.4 (5.0) 45.0 (8.1) p<0.001	 26 [b] 50 [b] p=0.16		 25.2 (18.9) 55.1 (20.4) <0.001		
SF-12/36 Physical Baseline value Endpoint value P-value			**SF-36** 40 [b] 48 [b] p<0.05	**SF-36** 37.3 (7.2) 49.7 (8.3) p<0.0001	**SF-12** 38.9 (7.3) 44.0 (5.5) 0.001		 38.6 (6.6) 46.6 (6.8)
SF-12/36 Mental Baseline value Endpoint value Change value P-value			**SF-36** 50 [b] 55 [b] NR p=ns	**SF-36** 49.7 (10.8) 53.5 (7.5) NR p=0.0032	**SF-12** 55.5 (9.4) 55.2 (8.2) p<0.34		SF12 54.0 (11.7) 55.8 (8.0)
SF-12 overall Baseline value Endpoint value P-value						 43.5 (5.6) 46.6 (5.9) 0.041	

[a] Outcomes assessed at 2 years, not mean follow-up of 2.9 years, results described as mean (95% CI). [b] estimated from figure.

Subgroups: medial vs lateral MAT

Nine studies [253 256 254 264 269 272 276 283 286] assessed medial and lateral MATs separately (Table 42) for at least one functional or quality of life outcome but only one [276] found statistically significant differences in functional outcomes or quality of life between medial and lateral MAT, in a group of patients having combined MAT and anterior cruciate ligament reconstruction, with only seven patients in the lateral group. In an earlier paper from the same group, Cole et al [256] commented that the lateral subgroup showed a trend toward greater improvements than the medial subgroup on nearly all knee scoring scales.

Table 42: Medial and lateral MAT subgroups: functional outcomes and quality of life

Study	Medial		Lateral		P value
Abat et al [253]	**Only-suture, n=33**		**Bony-fixation, n=55**		
	Medial n=14	**Lateral n=19**	**Medial n=25**	**Lateral n=30**	
Lysholm, mean (SD) Endpoint value	88.4 (7.5)	89 (9.2)	89.2 (7.4)	93.2 (6.2)	p=ns
Tegner, median (range) Endpoint value	6 (3–8)	6 (3–8)	6 (3–9)	7 (1–9)	p=ns
Cole et al [256]	**Medial, n=25**		**Lateral, n=15**		
Lysholm, mean					
Baseline value	52.11		52.77		p>0.05
Endpoint value	69.20		75.60		P>0.05
% change	32.8		43.3		
P-value	0.001		0.013		
IKDC, mean					
Baseline value	45.71		46.86		p>0.05
Endpoint value	60.62		69.55		P>0.05
% change	36.3		48.4		
P-value	0.002		0.005		
Tegner, mean					
Baseline value	4.45		5.86		p>0.05
Endpoint value	5.88		7.40		P>0.05
% change	32.1		26.3		
P-value	0.091		0.261		
SF-36 Physical, mean					
Baseline value	38.84		39.31		p>0.05
Endpoint value	46.15		52.23		P>0.05
% change	18.8		32.29		
P-value	0.052		0.004		
SF-36 Mental, mean					
Baseline value	52.16		49.23		p>0.05
Endpoint value	55.64		55.11		P>0.05
% change	6.7		11.9		
P-value	0.307		0.154		
Saltzman et al [277]	**MAT+ACL reconstruction, n=40**				
	Medial n=33		**Lateral n=7**		
IKDC, mean (SD)	56 (22)		75 (14)		0.06
KOOS ADL, mean (SD)	80 (21)		98 (4)		0.05
KOOS sport, mean (SD)	44 (28)		67 (17)		0.07
KOOS QoL mean (SD)	40 (24)		70 (14)		<0.01
WOMAC function mean (SD)	11 (11)		1.3 (2.8)		0.03
WOMAC total, mean (SD)	20 (16)		4.8 (6.2)		0.04
González-Lucena et al [254]	**Medial MAT, n=14**		**Lateral MAT, n=19**		**P-value**
Lysholm, mean (SD) Endpoint value	88.37 (7.5)		89 (9.2)		0.64

Tegner, mean (SD) Endpoint value	5 (1.53)	6 (2)		>0.99
LaPrade et al [264]	**Medial MAT, n=19**	**Lateral MAT, n=21**		
IKDC subjective scores Baseline value Endpoint value P-value	51.2 68.2 <0.001	57.6 76.6 (n=15) <0.001		
Marcacci et al [269]	**Medial MAT, n=16**	**Lateral MAT, n=16**		
Lysholm, mean (SD) Baseline value Endpoint value	59.9 (19.6) 83.3 (13.7)	59.7 (17.4) 86.4 (9.7)		p=ns
IKDC, mean (SD) Baseline value Endpoint value	48.3 (19.8) 77.1 (18.5)	46.6 (21.9) 77.4 (12.5)		p=ns
Tegner activity level, median (IQR) Baseline value Endpoint value	3 (2-5) 4 (3-7)	4 (3-4) 5 (4-6)		p=ns
SF-36 PCS, mean (SD) Baseline value Endpoint value	36.1 (7.8) 49.4 (8.9)	38.5 (7.8) 47.6 (7.4)		p=ns
SF-36 MCS, mean (SD) Baseline value Endpoint value	56.1 (6.9) 56.6 (5.5)	43.3 (9.8) 50.4 (8.4)		p=ns
Rue et al [272]	**Medial, n=20 (7 MAT+ACI, 13 MAT+OA)**	**Lateral, n=11 (9 MAT+ACI, 2 MAT+OA)**		
Lyshom, mean (SD) Endpoint value	83.8 (9.5)	76.0 (13.1)		
IKDC, mean (SD) Endpoint value	79.7 (11.2)	73.3 (10.3)		
Tegner, mean (SD) Endpoint value	6.8 (1.2)	7.6 (1.8)		
SF-36 Physical, mean (SD) Endpoint value	44.8 (4.2)	46.1 (3.0)		
SF-36 Mental, mean (SD) Endpoint value	52.6 (6.7)	56.3 (6.3)		
Van Arkel et al [283]	**Medial n=17**	**Lateral, n=34**	**Both n=6**	
Lysholm score, Mean (range) Baseline value[a] Endpoint value p-value	44.0 (15-86) 55.36 (23-90) 0.134	37.10 (6-65) 63.9 (21-91) 0.000	37 (15 to 56) 77 (48 to 99) NR	
KOOS, mean, 13.8 years Pain Symptoms Function in daily living Sport and recreation Quality of life	52.64 (19-100) 54.09 (29-100) 61.09 (34-100) 23.18 (0-100) 27.36 (0-100)	66.70 (22-100) 60.10 (32-96) 72.75 (37-100) 40.00 (0-100) 43.00 (6-100)		0.143 0.448 0.219 0.132 0.127
Verdonk et al [286]	**Medial, n=39 allografts**	**Lateral, n=61 allografts**		

Modified HSS pain score, mean (SD), Baseline value Endpoint value P-value	 11.9 (3.9) 34.2 (17.2) 0.000	 14.8 (9.3) 42.7 (10.3) 0.000	
Modified HSS function score, mean (SD), Baseline value Endpoint value P-value	 58.6 (23.6) 83.7 (25.14) 0.000	 61.1 (18.4) 91.64 (17.4) 0.000	
	Isolated medial MATs (20)	**Isolated lateral MATs(49)**	
Modified HHS pain score Mean (SD) Baseline Endpoint P value	 11.6 (7.7) 33.5 (18.6) P = 0.001	 15.3 (9.4) 42.7 (10.1) P =0.000	
Modified HSS function score mean (SD) Baseline Endpoint P value	 58.7 (27.0) 83.7 (26.3) P = 0.014	 61.5 (19.5) 92.6 (15.9) P = 0.000	
Failure	35%	18%	
Time to failure mean (SD)	6.8 years (4.6)	4.8 (2.9)	
Proportion surviving (rounded) 5 years 10 years 15 years	 84% 72% 27%	 91% 67% 67%	

[a]Baselines in earlier publications reported to be lateral: 33 (5 to 73); Medial 39 (15 to 76). No statistically significant differences between lateral and medial.

Eight studies [261] [266] [216, 267] [276] [278, 284] [286] reported survival outcomes for medial and lateral MAT, six showing no statistically significant differences. Parkinson et al [216] found increased graft survival with lateral MAT (89% at 5 years versus 62% for medial, p = 0.026) (Tables 43 and 44). Kim et al [261] reported 13% of failures in lateral MAT compared to 3.7% in medial MAT but the medial figure was based on only one patient, and some patients were classed as failures because of MRI findings despite satisfactory Lysholm scores. Van der Wal et al [284] did not present statistical analysis, but failure rates were higher in the medial subgroup (35%) than the lateral (25%) and time to failures was shorter (mean 82 months medial versus 161 months lateral). Verdonk et al [286]reported 28% failures in medial MAT compared to 16% in lateral MAT but the difference was not statistically significant.

Table 43: Medial and lateral MAT subgroups: survival, prospective studies

Noyes and Barber-Westin [266] [1]	**Medial MAT, n=41 (transplants)**	**Lateral MAT, n=31 (transplants)**	**P-value**
Survival, %, mean (95% CI) 2 years 5 years 7 years 10 years 15 years	 85 (70, 94) 75 (59, 87) 65 (48, 78) 41 (27, 58) 14 (5, 29)	 84 (65, 94) 80.5 (62, 92) 74 (55, 87) 50 (32, 68) 29 (15, 50)	NS
Mean (SD) time to failure requiring reoperation, years	8.2 (5)	7.7 (5)	
Parkinson et al [216]	**Medial, n=25**	**Lateral, n=100**	
5 year survival, %	62	89	0.026
Lateral vs Medial, HR (95% CI) survival	0.24 (0.07, 0.84), p=0.03		
Failures	6/25 (24)	7/99 (7)	
Stone et al [278]	**Medial, n=85**	**Lateral, n=34**	
K-M overall mean survival	9.9 years (SD 0.5, 95% CI 9.0 to 10.8, 1.3 to 12.3 years)	10.2 years (SD 0.8, 95% CI 8.6, 11.7, 2 months to 12.3 years)	
	medial versus lateral HR 1.11 (p=0.848)		

[1] Short-term results Noyes et al [267]

Table 44: Medial and lateral MAT subgroups: failure, survival and reoperations, retrospective studies

Study	Medial	Lateral	P value
Saltzman et al [277]	**MAT+ACL reconstruction, n=40**		
	Medial n=33	**Lateral n=7**	
No. of reoperations, mean (SD)	1.1 (0.8)	0 (0)	<0.01
Time to reoperation, y, mean (SD)	3.8 (4.2)	NA	NA
Athletes returned to plan, n (%)	5 (15)	4 (57)	0.68
Graft failure, n (%)	8 (24)	0 (0)	0.15

Van Arkel et al [283]	**Medial n=17**	**Lateral, n=34**	**Both n=6**	
Failure, n (%) 13.8 years	8 (35)	10 (25)		
Time to failure, months, mean (range)	82 (51-97)	161 (100-208)		
Subgroups at 60 months:				
Cumulative survival rate (worst case and clinical criteria), % (95% CI)	50 (55, 83)	76 (82, 92)	67 (58, 94)	
Mean survival time, months	69	111	89	
Cumulative allograft survival, % (95% CI) (success rate)	63 (55, 83)	88 (85, 92)	67 (58, 94)	

Verdonk et al [286]	**Medial, n=39 allografts**	**Lateral, n=61 allografts**	
Failure, n/N (%)	11/39 (28)	10/61 (16)	
Time to failure, years, mean (SD)	6.0 (3.8)	4.8 (2.8)	
mean cumulative survival time, years mean (95% CI)	11.6 (10.1, 13.1)	11.6 (10.3, 12.9)	p=0.733
Cumulative Survival Rate, % (SD) - 5 years - 10 years - 14 years	 86.2 (5.7) 74.2 (7.4) 52.8 (14.4)	 90.2 (4.2) 69.8 (9.7) 69.8 (9.7)	
Kim et al [261]	**Medial n=27 knees**	**Lateral n=83 knees**	
Failure, %	3.7	13.3	
Stone et al [281]	**Medial, n=37**	**Lateral, n=49**	
Failure %	27	41.7	1.00

Subgroups: combined procedures

Eight studies considered concurrent procedures [256] [254] [264] [269] [272] [216, 266] [257] – Tables 45 and 46.

Table 45: Combined procedures subgroups: functional outcomes and quality of life

Study	Procedures		P-value
Abrams et al [257]	**Combined MAT and OCA** Lysholm - Baseline 41.9 (16.1) - Endpoint 63.6 (24.1 - P <0.001 IKDC - Baseline 32.9 (11.4) - Endpoint 55.3 (23.6 - P < 0.001 KOOS - Baseline 42.5 (11.7) - Endpoint 62.7 (21.0) - P < 0.001		
Cole et al [256]	**Isolated MAT, n=21**	**Combined, n=19**	
Lyshom, mean			
Baseline value	47.94	57.4	p>0.05
Endpoint value	68.05	75.53	P>0.05
% change	41.9	31.6	
P-value	0.002	0.006	
IKDC, mean			
Baseline value	43.90	48.75	p>0.05
Endpoint value	61.77	66.46	P>0.05
% change	40.7	36.3	
P-value	0.002	0.004	
Tegner, mean			
Baseline value	5.39	4.63	p>0.05
Endpoint value	6.14	6.83	P>0.05
% change	13.9	47.5	
P-value	0.326	0.032	
SF-36 Physical, mean			
Baseline value	38.06	40.29	p>0.05
Endpoint value	46.86	50.20	P>0.05
% change	23.1	24.6	
P-value	0.007	0.050	
SF-36 Mental, mean			
Baseline value	46.56	56.64	p>0.05
Endpoint value	53.37	57.62	P>0.05
% change	14.6	1.73	
P-value	0.125	0.373	
González-Lucena et al [254]	**ACL reconstruction, n=8**	**Microfracture, n=8**	**P-value**
Lysholm score, mean Endpoint	86.6	90	>0.05 among subgroups and total sample mean 88.6
LaPrade et al [264]	MAT alone n = 19	MAT and other procedures n=21, including ACL 10, microfracture 5, OCA 3, osteotomy 3	No significant difference in outcomes

Marcacci et al [269]	MAT alone n=22	MAT + n= 10. ACL 4, osteotomy 6	No significant difference in outcomes
Rue et al [272]	**MAT+ACI, n=16 transplants**	**MAT+OA, n=15 transplants**	
Lyshom, mean (SD) Baseline value Endpoint value P-value	 55.0 (16.0) 79.4 (11.9) <0.001	 42.0 (14.5) 68.2 (21.3) 0.001	 P = 0.037
IKDC, mean (SD) Baseline value Endpoint value P-value	 45.5 (8.2) 76.0 (10.8) <0.001	 31.4 (12.8) 57.1 (17.8) <0.001	 P = 0.002 P = 0.0024
Tegner, mean (SD) Baseline value Endpoint value P-value	 5.5 (2.9) 7.3 (1.5) 0.026	 4.4 (3.7) 6.2 (2.9) 0.03	
SF-12 Physical, mean (SD) Baseline value Endpoint value P-value	 40.6 (6.3) 45.6 (3.5) 0.009	 37.0 (8.2) 42.2 (6.9) 0.081	
SF-12 Mental, mean (SD) Baseline value Endpoint value % change P-value	 58.2 (6.4) 54.7 (6.5) -6.0 0.159	 52.6 (11.3) 55.7 (9.9) 5.9 0.135	 p=0.038

Table 46: Combined procedures subgroups: survival

Noyes and Barber-Westin [266]	**Concurrent osteochondral autograft, n=52 (transplants)**	**No concurrent osteochondral autograft, n=20 (transplants)**	
Survival %, mean (95% CI) at 2 years 5 years 7 years 10 years 15 years	 88 (76 to 95) 78 (64 to 88) 76 (62 to 86) 55 (41 to 69) 19 (10 to 33)	 75 (50 to 90) 75 (50 to 90) 50 (28 to 72) 20 (7 to 44) 20 (7 to 44)	p<0.05
Parkinson et al [216]	**N not reported**		
HR for additional procedures versus isolated MAT	1.62 (95% CI 0.31, 8.43)	p=0.56	

Most studies found no statistically significant differences between those undergoing isolated MAT or MAT combined with other concurrent procedures on either functional, quality of life or survival estimates. However, Noyes et al [266] found a statistically significantly poorer survival time in knees that required a concurrent osteochondral autograft transfer, compared to those that did not. Rue et al [272] noted differences in IKDC score between those undergoing MAT+ACI and MAT + OA transplantation, however there was also an imbalance in scores at baseline. Noyes et al [267]

also reported analysis of those having ligament reconstruction or osteochondal autgrafts, and those having MAT alone, and found no significant differences.

Meniscectomy versus no meniscectomy

Li et al [291] compared two groups of meniscectomised patients, one group having MAT and the other not. About half of the MAT group had allografts inserted at the time of meniscectomy. The rest had MAT on average 3 years later because of pain in the knee. At average follow-up of 54 months (minimum 40 months), clinical results were similar but there was less radiographic change in the MAT group. The study was too small and too short duration to compare immediate versus delayed MAT.

Return to sport

Saltzman et al [275] and Stone et al [281] reported return to sport. In the subgroup having concomitant MAT and ACL reconstruction in the Saltzman et al study [277], 19 participants self-identified as athletes and 50% of these returned to sports, 39% at the same level as previously. Of 10 who had been involved in competitive sport, 50% returned to sport at the same level. This study was assessed as fair quality, although note that the sample for these outcomes was small. Stone et al [281] reported that 74% of the 49 participants in their study were able to participate in sport.

Adverse events

Complications were generally infrequent. Van Arkel et al [283] reported no major complications and only five minor ones amongst 63 grafts, these being irritation around non-absorbable sutures. Three studies reported a need to resolve flexion problems by manipulation or arthrolysis a few weeks after MAT in four of 38 patients [267], one of 32 patients [269] and one of 32 patients [271]. Stone et al [278] reported four infections amongst 115 patients, and Saltzman et al [275] reported two minor infections in 40 patients. LaPrade et al [264] reported one late infection but it appears unrelated.

Kempshall et al [217] reported major complications in 17% of the 'chondral surface good' group and 38% of the 'chondral surface bare' group, this included tear of the allograft in 13% and 31% respectively. Abat at al [253] reported total complication rates of 33.3% of the only-suture group and 16.4% of the bony fixation group. Three studies reported that no complications occurred [257] [256] [272] and in one study adverse events were not reported [264].

Assessing the cost-effectiveness of meniscal allograft transplantation

The benefits of MAT could include symptomatic relief and restoration of at least some previous activities, which will be reflected in utility values, and in the longer-term, prevention or delay of osteoarthritis, and avoidance or postponement of some knee replacements, with resulting savings.

The costs include the initial procedure, the cost of the allograft, and any subsequent surgery, including arthroscopic debridement if the graft has to be removed, and possibly insertion of a second MAT.

For cost-effectiveness analysis, data are needed for both patients having MAT, and a comparison group that does not have MAT after meniscectomy, as follow;

- Quality of life expressed as a utility measure using a generic preference based measure such as EQ-5D-5L, or a clinical outcome score such as WOMAC, from which we can map to EQ-5D. This captures symptomatic relief and return to activities. (Though EQ-5D may not capture all the utility of return to sport since it is based more on activities of daily living.) Increasing OA would reduce quality of life over time.
- Costs of MAT including rehabilitation.
- Costs of MAT failure, including if appropriate, repeat MAT. A second MAT in the same compartment is uncommon [270] [266] [276] [281] [285]. However if a first MAT in a young person lasted for, say, 10 years, providing symptomatic relief, there could be a case for a repeat MAT, perhaps as an interim intervention pending knee arthroplasty.

- Costs of conservative care for people not having MAT, including physiotherapy and drug costs. In this case, "physiotherapy" would need to be carefully defined, since it is an umbrella term covering many different forms of treatment, and a personalised knee therapy intervention for the meniscal deficient knee may be more effective. (See pilot RCT by Smith et al [292]).
- Costs of advanced OA, principally TKA, for both groups. This will depend on proportions having TKA.

However, data are lacking on;

- What proportion of people who don't get MAT, develop advanced OA requiring TKA, and when. It is assumed that surgeons will be reluctant to do TKA before age 55.
- What proportion of people who do get MAT, develop advanced OA requiring TKA, and when.

Almost all the studies of MAT are observational ones with no non-MAT control groups. However Smith et al [292] have reported the results of a pilot RCT of MAT versus personalised physiotherapy. At 12 months, KOOS scores improved in both groups but the improvement in the MAT group was roughly double that in the physiotherapy group - a difference of 12 in composite KOOS (p = 0.03). Other scores improved more in the MAT group but without reaching statistical significance. Smith et al advocate caution in interpretation due to small numbers (21 randomised, plus a preference group of 15), the short follow-up, and possible effects of the three osteotomies in the MAT group but none in the physiotherapy group. They use the data to estimate that a trial with 50 patients in each arm would be required to give a definitive result.

We found no published cost-effectiveness studies of MAT versus conservative care. A recent review of cost-effectiveness studies for non-osteoarthritic knee pain conditions by Afzali and colleagues [293] found only one study of MAT, and was the one by Ramme et al mentioned above in discoid cartilages)[235].

Discussion

There seems to be no doubt that meniscectomy, whether total or partial, leads to OA in the longer term. However, it is not yet proven whether MAT is chondroprotective. With the data currently available, it does not appear possible to do a full assessment of the cost-effectiveness of MAT. The main problem is the lack of control groups, having active conservative care. MAT is probably better, but for cost-effectiveness analysis we need to know the effect size – how much better is it?

The people who get significant problems after meniscectomy may be a small subset, perhaps only 10-20% of all having meniscectomy. Those who present with significant symptoms with or without radiological evidence of OA at 5-10 years after meniscectomy, may have other risk factors. It is assumed that people having MAT have had a traumatic meniscal tear and subsequent meniscectomy, and that they do not come from the older group with degenerate menisci, whose natural history is different (and who should not be used as a natural history comparison group).

To compare outcomes of MAT and non-MAT, data are needed on how people are selected for MAT in order to identify a comparable group of people in non-MAT natural history studies. In some MAT studies, patients with more severe knee problems such as existing OA, or advanced KL grades, are excluded. So some non-MAT people may have a more severe mix of knee problems. If so, comparing a MAT cohort with people who do not get MAT after meniscectomy, may favour MAT. But more likely, if the MAT group are a small subset of all people who have had meniscectomy, and who are doing worse, then a comparison with a non-MAT group may under-estimate the benefits of MAT.

We may also need to consider how to classify MAT. One suggestion (C Harner, personal communication May 2018) is to consider categories as follow;

- Isolated MAT, medial and lateral
- MAT combined with OCA
- MAT combined with osteotomies (femoral or tibial)
- MAT combined with ligament reconstruction

The likelihood of success is greater in those with less damage to the articular cartilage. A particularly difficult group are young people with ICRS grade 3 lesions in whom conservative treatment has failed, and who are much too young for knee replacement. Two options have been tried. One is the "biological knee replacement" combining MAT with ACI as reported by Bhosale et al [294] from Oswestry, but with a series of only eight patients. The other is to combine MAT with osteochondral allografts, as reported by Abrams et al [257] and Frank et al. [45]

However, the results of the study by Kempshall et al and Parkinson et al [216, 217] show that in patients with more severe "bone on bone" defects, MAT may not be as successful as in people with lesser defects, but can still provide benefit. It is possible that MAT may be both less successful and more cost-effective in the more severe group because they have more to gain. The gains in symptom scores were of similar magnitude but the severe group started from a lower baseline.

A short-term before and after analysis could compare quality of life using an instrument that can be converted to a utility measure, such as WOMAC or SF-12, and assessing the cost per quality adjusted life year (QALY) gained from the quality of life gains. However, the improvements may be due to MAT, or associated rehabilitation, or some natural recovery, or by patients learning to live with the problem, for example by reducing activities. Data are lacking data on what benefits the non-MAT measures might provide for non-MAT patients. They would be expected to benefit from physiotherapy, if they get it. But if the MAT group got physiotherapy and the non-MAT group did not, it would not be clear whether any benefits were due to MAT or physiotherapy.

So a before and after analysis could be misleading, and favourable to MAT. However the pilot RCT by Smith et al [292] reported that MAT had advantages over conservative care with personalised physiotherapy.

In summary, with the data currently available, it does not appear possible to do a full assessment of the cost-effectiveness of MAT.

A very good study by Bendich et al [215] has addressed this problem. They noted that there was uncertainty about the chondroprotective effect of MAT [246 214 285]. They then asked how effective MAT would have to be, to be cost-effective. They start by assuming that after meniscectomy, progression to severe OA (bad enough for TKA to be considered) would be 1.8% a year, based on the study by Englund et al [295], but they then do sensitivity analyses around that figure, with higher and lower progression rates. In their primary "base case" analysis, patients are aged 30, with no OA, and BMI 20. They test various other scenarios, with older or heavier patients, and different ages at which TKA would be performed. They also test different costs of MAT, TKA and of non-operative care.

In their base case, they estimate that MAT would have to reduce progression to severe OA by 31%, from 1.8% a year to 1.2% a year. However in patients with higher BMIs, who are at increased risk of progression to OA, the reductions need only be 16% in the BMI 25-30 group, and 10% in the BMI over 30 group, for MAT to be cost-effective. Their base case age was 30. In patients aged 20-29 (who would have to wait much longer for TKA), the reduction in progression for MAT to be cost-effective was only 25%, whereas in the 40-49 age group, the reduction in progression would need to be 41%.

The costs used were from the USA, including TKA cost of $26,452, and only slightly higher for revision TKA. Costs in other countries would be different. They assumed cost of MAT to be $8202.

In their base case, they assumed no OA, whereas we know that many people who have needed meniscectomy have sustained articular cartilage damage. In those people, progression to OA would be faster, and cost-effectiveness of MAT greater. They do not give details of interval between meniscectomy and MAT. Their benefits focus on reducing progression to OA and joint replacement, rather than on relief of symptoms after meniscectomy.

The pilot RCT by Smith et al [292] showed greater benefit with MAT than personalised physiotherapy and it may be that MAT could be shown to be cost-effective based on utility gain from symptom relief alone, with taking into account future cost of TKA avoided. A similar but much larger and longer trial is needed to confirm this.

As outlined above, there appears to be a subgroup that do particularly badly after meniscal tears and subsequent meniscectomy. MAT would be much more cost-effective in this group, so a high research priority is how to identify

them at or soon after meniscectomy, and to see if intervention soon after meniscectomy gave better result than waiting for symptoms to develop.

Research priorities include the need for randomised controlled trial evidence for the effectiveness of MAT compared with conservative care in short-term effectiveness, and also the long-term potential to change the natural history after meniscal loss. Further research is also warranted on the best choice of graft, surgical technique, and optimal rehabilitation after surgery.

The evidence on MAT comes from a relatively small number of centres that have developed considerable expertise over many years. One issue with such evidence is whether results in other centres would be as good

Conclusions

There were three issues to be considered;

1. Does meniscal deficiency lead to early osteoarthritis? Yes.
2. Does MAT prevent or delay OA after meniscectomy? There is a lack of good evidence on this, so the verdict at present is “not proven”.
3. Is MAT an effective and cost-effective way of relieving continuing symptoms after meniscectomy? It appears effective, but the effectiveness of MAT compared to conservative management is uncertain, with only the one small RCT providing short-term evidence.

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Appendix 1: Literature searches

Ovid Medline Search strategy

1. exp Allografts/

2. allograft*.mp.

3. 1 or 2

4. (osteochondral or cartilage or chondrocyte* or osteoarticular or chondral or articular or condyle or tibia* or knee* or patell* or menisc* or ligament* or femoral or femur or patellofemoral).tw.

5. exp Cartilage, Articular/su [Surgery]

6. exp Cartilage/tr [Transplantation]

7. chondrocytes/tr [Transplantation]

8. Knee/su [Surgery]

9. exp Knee Joint/su [Surgery]

10. exp Ligaments, Articular/su [Surgery]

11. exp Menisci, Tibial/su, tr [Surgery, Transplantation]

12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. 3 and 12

14. (letter or editorial).pt.

15. 13 not 14

16. limit 15 to english language

17. limit 16 to yr="2000 -Current"

The Ovid Medline search strategy above was adapted as appropriate for Ovid Embase, Web of Science and the Cochrane Library. The searches were last run on February 15th, 2018.

All records were downloaded into the bibliographic database Endnote. After deduplication, 5013 articles were screened by one reviewer for obvious exclusions. The title and abstracts of the remaining 3468 articles were screened independently by two reviewers. The full texts of 815 articles were then obtained for further scrutiny.

The search was designed to be very sensitive in order to include all study designs and to retrieve articles for clinical effectiveness, costs and economics, natural history and prognosis. The searches included articles published as full text and conference abstracts, and were limited to English language articles only. The reference lists of systematic reviews and included studies were also checked.

Appendix 2: Retrospective studies in ACL

Reference	Aim	Population	Study details	Key results (from abstract)
ACL – primary				
Barber 2014[296]	To compare clinical outcomes and revision rates for ACL reconstructions using bone-patellar tendon-bone (BPTB) allografts versus BPTB autografts in a population of patients aged 25 and younger.	Patients ≤25 years or younger undergoing an ACL reconstruction with radiographically proven closed or nearly closed growth plates and ≥follow-up 24 months. Patients with a history of patellar tendinopathy, jumper's knee, or Osgood Schlatter's disease, and participants in sports including high jump, team handball, and basketball were included. Revision surgery was not an exclusion criterion. Two groups (patient preference): allograft and autograft. 2001 - 2012	Sample size: 81 (28 allograft, 53 autograft) Follow-up: 34 months (allograft 37 [range 24-71]; autograft 31 [24-132] months) Data collection: not reported	7.1% allografts and 9.4% autografts failed. Mean Cincinnati scores improved from 54.6 and 39.5 (allografts and autografts, respectively) to 86.2 and 85.1. Mean Lysholm scores improved from 60.3 and 44.8 (allografts and autografts, respectively) to 89.9 and 87.0. IKDC activity scores were 2.9 (allografts) and 3.1 (autografts) postoperatively (P =0.32).
Carter 2016[297]	To evaluate the outcome for patients younger than 25 years who had ACL reconstructions with allograft tissue	Those who received ACL reconstruction with an allograft for an isolated ACL tear or ACL tear plus meniscectomy or repair of meniscal tear during a 3-year period.	Sample size: 42 Follow-up: 65 (range 33-99) months Data collection: not reported	IKDC subjective score was 90.2 (15.0) and Lysholm score 90.0 (11)
Kane 2016 [298]	To evaluate the clinical outcomes and revision rates of skeletally mature patients aged 25 years or younger who have undergone either BPTB autograft or deep-frozen, non-irradiated BPTB allograft ACL reconstruction by a single surgeon.	Skeletally mature patients aged ≤25 years undergoing ACL reconstruction between 2008 and 2012, primary ACL reconstruction with either BPTB autograft or BPTB allograft, and closed physes and minimum 2-years follow-up.	Sample size: 119 (59 allograft; 60 autograft) Follow-up: minimum 2 years Data collection: not reported	The median Lysholm scores were 95 (40–100) in the allograft group and 95 (68–100) in the autograft group, p=ns. The median IKDC scores were 95.4 (54.0–100) and 95.4 (72.4–100) in the allograft and autograft groups, respectively, p=ns. There were 12 allograft versus one autograft patients required ACL revision (P = 0.005).
Kim 2017[299]	to compare stability, functional outcome, and second-look arthroscopic findings after ACL	Having ACL reconstruction and had second look arthroscopy, 2010 – 2014. Two groups, remnant-	Sample size: 50 (allograft 25; autograft 25)	There was no significant intergroup difference in stability, clinical outcome, and second-look arthroscopic findings.

	reconstruction between remnant-preserving tibialis tendon allograft and remnant-sacrificing hamstring tendon autograft.	preserving tibialis tendon allograft matched with those having remnant sacrificing hamstring tendon autograft.	Follow-up: allograft 26.8 (24.0–52.3) months; autograft 28.9 (24.0–59.5) months Data collection: not reported	
Kim 2014[300]	to compare the outcomes after ACL reconstruction using Achilles tendon allografts and tibialis anterior (TA) tendon allografts with respect to objective knee testing measures, second-look arthroscopy and femoral tunnel enlargement.	Those who underwent an ACL reconstruction with an Achilles or TA tendon allograft and aged 20–50 years. 2000 - 2006	Sample size: 131 (81 knees Achilles allograft; 50 knees tibialis anterior allograft) Follow-up: 7.5 (5.5 – 10.9) years Data collection: not reported	No significant differences were observed between the two groups with respect to IKDC, Lysholm or Tegner activity scores.
Kim 2014[301]	to compare the clinical outcomes of ACL reconstruction between smokers and non-smokers and to find an optimal graft in ACL reconstruction with regard to clinical outcomes for smoking patients.	Age >18 years, primary single bundle ACL reconstruction, isolated ACL injury without a concomitant ligamentous injury, unilateral ACL injury without a contralateral knee injury, maintained hoop function with an intact or partially resected meniscus, no chondral lesion higher than grade 2 Outerbridge grading system, no malalignment of the lower extremity, no previous surgery to the affected knee. Two groups never smokers (group 1) and current smokers (group 2); subgroups: BPTB autograft, quadriceps tendon–bone autograft, hamstring tendon autograft, Achilles tendon-bone allograft . 2002 -2009	Sample size: 487 (group 1 322, allograft subgroup 19; group 2 165, allograft subgroup 34) Follow-up: minimum 24 months Data collection: medical record review	The Achilles tendon–bone allograft showed the worst outcomes, with statistically significant mean differences for smoking patients in Lysholm knee score (81.05 [SD 2.82]), and IKDC subjective score (79.73 [4.29]) compared with autografts.

Mascarenhas 2010[302]	To compare patient-reported and objective outcomes in high-demand patients after ACL reconstruction with either patellar tendon allograft or autograft by use of a matched-pairs case-control experimental design	Patients who had undergone primary ACL reconstruction and reported that they participated in strenuous or very strenuous sporting activity 4 to 7 times per week. Autograft or allograft reconstruction based solely on patient preference, matched pairs.	Sample size: 38 (allograft 19, autograft 19) Follow-up: allograft mean 10.3 (SD 2.6) years, autograft mean 9.1 (SD 2.7) years Data collection: not reported	No statistically significant differences between groups in any of the patient-reported or objective outcome measures. More autograft patients reported that they were able to perform very strenuous activity without the sense of instability (73.7% v 36.8%, p=0.07). 63.2% of autograft patients were able to return to preinjury levels of sporting activity compared with 52.6% of allograft patients, p=ns. 84.2% of autograft patients and 63.2% of allograft patients were able to participate in strenuous or very strenuous sporting activity at follow-up, p=ns.
Noh 2017[303]	To assess the clinical and radiographic outcomes and the extent of synovial coverage on second-look arthroscopy of ACL reconstruction using a remnant-preserving and re-tensioning technique to easily cover the graft with a remnant.	ACL rupture and underwent ACL reconstruction with free tendon Achilles allograft with a 2-year minimum follow-up, and underwent second-look arthroscopy to evaluate the graft. Between 2011 and 2013. Indication: Lachman test grade of ≥2.	Sample size: 43 Follow-up: 25.7 (6.3) months Data collection: not reported	The mean Lysholm score was 54 (11) before surgery and 94 (5) at the last follow-up ($p < 0.001$). The median Tegner Activity Scale score was 6.5 (range 5–9) before injury and 6 (range 4–8) at the last follow-up ($p = 0.048$).
Mardani-Kivi 2016 [175]	To compare stability and function of the knee after ACL arthroscopic reconstruction by single-loop tibialis posterior allograft and four-strand hamstring tendon autograft.	Patients who underwent surgery (2007 – 2010); skeletally mature; aged 19–55 years; initially diagnosed ACL tear by MRI, at least two weeks' interval from the time of injury until full range of motion (ROM).	Sample size: 222 (allograft 104; autograft 118) Follow-up: allograft 55 (37-71) months, autograft 56 (36-72) months. Data collection: not reported	No significant differences were observed post-operatively regarding subjective evaluations. Time duration for return to former activity was similar in both groups. Post-operative paresthesia and numbness of medial aspect of the calf were observed for two months in 8 of the autograft group which persisted to the final visit in one case.
O'Brien 2014[304]	to obtain a matched comparison of patient-reported outcomes and graft-rupture	Undergone ACL reconstruction with either a BPTB or a TA allograft. 2006 – 2011.	Sample size: 40 (20 BPTB; 20 TA)	Mean Lysholm scores were 92.9 (BPTB) and 93.0 (TA), and mean IKDC scores were 92.6 (BPTB) and 90.3 (TA).

	rates of BPTB and TA allograft primary ACL reconstruction in patients younger than 30 years		Follow-up: 29.9 (SD 16.6) months BPTB; 25.6 (SD 13.1) months TA. Data collection: not reported	The differences were not statistically significant. Overall graft-rupture rates for the study period were 4.7% (BPTB) and 1.9% (TA) (P = 0.18). There was no statistically significant difference in patient-rated outcomes and graft-rupture rates between BPTB and TA allografts for ACL reconstruction
Revision ACL				
Battaglia 2007 [305]	To analyze the authors' experience with revision ACL surgery and determine the association between stability and functional results.	Having had revision ACL reconstruction in a single institution, 1991-2001	Sample size: 63 (of 95) Follow-up: 72.7 (range 36-158) months Data collection: operative records	Radiographic arthritis was identified in 25%. Return to sports occurred in 59% 25% required a second revision surgery.
Buda 2013[119]	To analyze the efficacy of an over-the-top ACL reconstruction technique plus extra-articular plasty using Achilles or tibialis posterior tendon allograft in restoring knee stability in patients with at least 2 failed previous ACL reconstructions.	ACL revision surgery with the OTT technique with lateral tenodesis using a fresh-frozen, nonirradiated Achilles or tibialis posterior Allograft; presence of at ≥2 failed previous ACL reconstructions with a correctly placed tibial tunnel, 2002-2008	Sample size: 24 Follow-up: 3.3 years (range, 2-7). Data collection: not reported	The mean IKDC subjective score at follow-up was 81.3 (SD 14.0). Of the 20 good results, 17 patients resumed sports activity at the preinjury level.
Chougule 2015[120]	To present intermediate-term clinical outcome after revision ACL reconstruction using semitendinosus allograft from donor less than 65 years old.	Revision ACL reconstructions using quadrupled semitendinosus allograft, 2003 to 2011	Sample size: 20 Follow-up: mean 6 (range 3–9) years Data collection: not reported	5% were re-revised for early graft failure and clinical instability, and 15 % had reoperations for other pathologies. Lysholm score improved from preoperatively 55.5 (SD11) points to postoperatively 89.7 (10) points, Tegner activity scale score improved from 2.7 (1.3) points to 7.1 (2.2) points. Level of Activity score improved from 3.6 ± 1.1 to 8.8 ± 1.6.

Grossman 2005[306]	To review our institution's experience with revision ACL reconstruction.	All who underwent revision ACL reconstruction between 1993-1999	Sample size: 23 (22 BPTB; 1 Achilles) Follow-up: 67 months (range 36-108) Data collection: not reported	No data for allograft only in abstract. Main text states there was no significant difference for subjective scores (Tegner, IKDC, Lysholm) between the allograft and the autograft group.
Keizer 2017[307]	To determine whether there is a difference in outcome after revision ACLR using a patellar tendon allograft compared to an ipsilateral patellar tendon autograft.	Underwent revision ACLR with patellar tendon allograft or ipsilateral patellar tendon autograft with a minimum follow-up of 1 year, between 2005 – 2015.	Sample size: 82 (36 allografts, 46 autografts) Follow-up: minimum 2 years Data collection: not stated	In patients with a minimum follow up rate of 2 years, rate of return to sport was 43.3% in the patellar tendon allograft versus 75.0% in the patellar tendon autograft group (p = 0.027). No differences in secondary study parameters were found.
Kievit 2013 [124]	To assess the degree of osteoarthritis, degree of laxity, and quality-of-life (QOL) scores in primary and revision ACL reconstruction	Those who underwent a revision ACL reconstruction with allograft material, 1997-2009. Compared to those who had undergone only 1 reconstruction of the knee in the same time period.	Sample size: 25 revision (27 primary) Follow-up: 5.3 years (revision); 5.1 years (primary) Data collection: hospital information system	Significantly worse outcomes were found in the following subscores of the KOOS: pain (median, 92 v 97; P=0.032), symptom (median, 86 v 96; P=0.015), activities of daily living (median, 94 v 100; P=0.02), sport (median, 50 v 85; P=0.006), and QOL (median, 56 v 81; P=0.001). Present-day health scores on the EQ-5D were worse for revision reconstruction patients (median, 70 v 80; P=0.009).
Legnani 2016[308]	To retrospectively compare the clinical outcome of contralateral hamstring tendon autografts vs. allografts for ACL revision surgery, specifically with regard to patient satisfaction, return to preinjury activity level, and postoperative functional outcomes	Those who underwent revision ACL reconstruction of a previously reconstructed ACL between 2004 – 2011. Inclusion criteria: failed primary ACL reconstruction, confirmed by recurrence of giving-way episodes as revealed by a positive Lachman and Pivot shift tests.	Sample size: 44 (allograft 21; autograft 23) Follow-up: 5.2 (range 2-7) years Data collection: not reported	No major complications were reported. There were no significant differences in IKDC and KOOS scores between the groups. The percentage of patients returning to pre-injury level was high in both groups and patients undergoing revision surgery with autografts experienced a quicker return to sports compared to patients who underwent allograft revision surgery.

Pascual-Garrido 2014 [128]	to report the outcomes, at 4 years follow-up, in revision ACL surgery using allografts in patients younger than 40 years old, and to compare soft tissue allografts to bone tendon allografts.	ACL reconstructions procedures classified as a revision surgery; aged <40 years. 1997 – 2007.	Sample size: 47 (patellar tendon allograft group 25; tibialis allograft group 22) Follow-up: 4.6 (SD 2.5) years (patellar tendon allograft group 4; tibialis allograft group 3.3) Data collection: review of records	Both subgroups experienced significant improvement in Lysholm and IKDC values, with no difference found between groups at final follow-up

Appendix 3: Systematic reviews in MAT

Quality assessment using NIH criteria

Review	Focused question	Eligibility criteria	Searches	Dual review	Validity	Study details	Publication bias	Heterogeneity
Dangelmajer et al 2017[243]	Y	Y	Y	CD	N	Y	N	NA
Smith et al 2016 + 2015[214, 244]	y	Y	Y	Y	N	Y	N	N
Samitier et al 2015[245]	Y	Y	Y	N	Y	Y	N	N
Rosso et al 2015[246]	Y	Y	Y	Y	Y	Y	N	N
ELAttar et al 2011[247]	Y	Y	Y	CD	Y	Y	N	N
Lee et al 2017[248]	Y[a]	y	y	Y	Y	Y	N	Y
Barber-Westin 2017[249]	Y	Y	Y	CD	Y	Y	N	NA
Bin et al 2017[250]	Y	Y	Y	Y	Y	Y	N (not possible)	Y
Jauregui et al 2017[251]	Y	Y	Y	N	N	Y	N	N
Lee et al 2017[252]	Y	Y	Y	CD	Y	Y	N	NA
De Bruycker et al 2017 [309]	Y	Partial	Partial	N	N	N	N	N

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported

1. Is the review based on a focused question that is adequately formulated and described?
2. Were eligibility criteria for included and excluded studies predefined and specified?
3. Did the literature search strategy use a comprehensive, systematic approach?
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?
5. Was the quality of each included study rated?
6. Were the included studies listed along with important characteristics and results of each study?
7. Was publication bias assessed?
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)

[a]question was to assess differences between MAT in isolation versus MAT in combination with other procedures.

Results	Conclusions
Dangelmajer et al 2017[243] Aim to compare meniscal transplants and scaffolds	

Meniscal Allograft Transplantation. 15 articles. Follow-up range 24.9 months – 15 years Overall failure rate ranged from 0% to 33.3% (average 18.7%) Overall reported operation rate ranged from 0 – 45.3% (average 31.3%). In one study 58% reported no increase in osteoarthritis, 42% slight to moderate increase (follow-up between 5-15 years). Meniscal scaffold: 7 articles Follow-up 12 months – 11 years Average failure rate of 5.6% (ranged from 0% to 17.3%) Average reoperation rate was 6.9% (ranged from 4.2% to 9.5%).	"Although meniscal allograft transplantation is associated with high reoperation and failure rates, the limited number of studies on both MAT and scaffolds and mainly short-term results of scaffold studies make it difficult to make an objective comparison."
Smith et al 2016[214] Aim to assess meniscal allograft transplantation in symptomatic meniscal deficient knees	
In 35 studies, with mean follow-up of 5.1 years (range 1-20 years): Lysholm scores improved from 55.7 to 81.3 IKDC scores from 47 to 70 Tegner activity scores from 3.1 to 4.7 Mean failure rate was 10.9 % at 4.8 years Mean complication rate was 13.6 % at 4.7 years. Radiological findings (not extracted). Joint space loss (not extracted) Kellgren and Lawrence scores, 3 studies: no change in one study (8.8 years follow-up); no change in 28 and 1 grade worsening in 8 patients in one study (2.6 years follow-up); 5 with no change and 5 with progression at 3.3 years follow-up in one study. Fairbank's classification, 3 studies: varied results, not extracted. IKDC radiological scores, 2 studies: minimal changes at 2.8 years follow-up in one, 1 grade worsening in 1 of 8 in one (at 8.5 years follow-up). Articular cartilage change on MRI; 3 studies. (not extracted) Osteoarthritis progression: 1 study, no change in 32/34 patients at 2 years, at 10 years 15 had mild change and 5 moderate or severe progression. Meniscal extrusion, 18 studies (not extracted) Signal intensity, 10 studies (not extracted) Meniscal size and shape, 10 studies (not extracted) Meniscal healing, 6 studies (not extracted)	2015 review: "Meniscal allograft transplantation appears to be an effective intervention for patients with a symptomatic meniscal deficient knee. This should ideally be confirmed with a randomised controlled trial. There is not currently enough evidence to determine whether it is chondroprotective." 2016 review: "There is some evidence to support the hypothesis that meniscal allograft transplantation reduces the progression of osteoarthritis, although it is unlikely to be as effective as the native meniscus. If this is proven, there may be a role for prophylactic meniscal allograft transplantation in selected patients. Well-designed randomised controlled trials are needed to further test this hypothesis."

Samitier et al 2015[245] (2 publications, part 1 not relevant but includes some methodology, Part 2 reviewed here) Aim to review optimal timing for transplantation, outcomes, return to competition, associated procedures, and prevention of osteoarthritis (part 2).	
All studies included in this review were in the more recently published reviews (above) and therefore no results have been extracted.	"there is no evidence to support that MAT has to be performed at the same time or immediately after meniscectomy to prevent development of postmeniscectomy syndrome; (b) MAT successfully improves symptoms, function, and quality of life at 7-to-14 years of follow-up; (c) the overall failure rate (need for knee arthroplasty) is 10–29 % at long-term follow-up; (d) MAT allows return to same level of competition in 75–85 % of patients at short- to mid-term follow-up (only three studies level IV evidence with small sample size); (e) associated cartilage procedures or anterior cruciate ligament reconstruction to MAT does not worsen the results; (f) MAT may prevent progression of cartilage damaged at long-term follow-up, but may not prevent degeneration in previously healthy cartilage."
Rosso et al 2015[246] Aim to assess the quality of the published studies on MAT; the indications ; the methods used for preservation, sizing, and fixation of the allograft; and the clinical and radiographic outcomes of this procedure and its role in preventing osteoarthritis (knees)	
Indication and contraindications for MAT (not extracted) Graft preservation, sterilization and sizing (not extracted) Surgical techniques (not extracted) Rehabilitation protocols (not extracted) The weighted average Lysholm score increased from 55.5 (2.1) preoperatively to 82.7 (2.7) at the last follow-up (varied across studies). The weighted average overall VAS score for pain decreased from 6.4 (0.4) to 2.4 (0.4) at the last follow-up (varied across studies) States some authors described a worsening of the results over time. Weighted average of overall satisfaction was 81.6% (3.8), 14 studies Slightly shorter survival for medial MAT compared with lateral MAT (2 studies)	"Meniscal allograft transplantation seems to provide good clinical results at short-term and midterm follow-up, with improvement in knee function as well as acceptable complication and failure rates. Higher quality studies are necessary to better assess the potential chondroprotective effect of MAT and to identify differences in terms of outcomes between different surgical techniques."

No difference in clinical outcome of survivorship between isolated MAT and MAT combined with other procedures (no data, 13 studies). Comparisons with bone plugs and suture-only fixation (not extracted) Radiological, MRI and second look arthroscopic surgery (not extracted) Weighted average of complications: 10.6% (of complications: common tear 59.6%; synovitis or effusion 30.7%; superficial infections 6.25%; reduction in movement 2.8%; deep infection 0.6%) Weighted failure rate 8.7% (11 studies) Survival time was 9.9 – 11.6 years (2 studies); survival rate was 52.5% at 16 years in one study.	
ELAttar et al 2011[247]	
Mean follow-up 4.6 years (range 8 months – 20 years); 44 studies. Average Lysholm score 44 at baseline; 77 at last follow-up. Average Tenger activity score 3 at baseline; 5 at last follow-up. Overall pain VAS at baseline 48mm, at last follow-up 17mm. IKDC 84% normal or nearly normal at last follow-up 89% participants were satisfied with their outcome at last follow-up. Average original Coleman scores 45.9 ± 8.4 (range 25–59). Average modified Coleman scores 43.7 ± 9.1 (range 24–62). Failure ((sub)total destruction/removal of the graft with or without conversion to arthroplasty) rate per trial, 10.6% Complication rate overall mean, 21.3% (128 complications reported). Radiological outcomes (not data extracted) Second-look arthroscopy (not data extracted)	"All studies reported a continuously satisfactory outcome with restoration of working capacity in these active patients. The complication and failure rates are considered acceptable by all authors. Salvage procedures included osteotomy and arthroplasty without secondary difficulties. Meniscal allograft transplantation can be considered as safe and reliable for the treatment of refractory post-meniscectomy symptoms in selected patients."
Lee et al 2017[290] Aim to evaluate whether there is a difference in clinical outcomes between isolated MAT and MAT combined with other procedures (combined MAT).	
Mean follow-up ranged from 24.9 to 180 months; 24 studies Lysholm score, 10 studies: isolated MAT vs combined MAT mean difference -2.19 points (95% CI, –5.92, 1.55; P = 0.25; I^2 28%) Tegner score, 6 studies: isolated MAT vs combined MAT mean difference -0.16 points (95% CI -0.54, 0.22; p=0.41; I^2 4%) IKDC subjective: isolated MAT vs combined MAT mean difference -1.15 (95% CI, –5.67, 3.37; P = 0.62; I^2 34%)	"Overall, there seems to be no significant difference between the postoperative PROs in terms of isolated MAT and combined MAT. However, more data are required to verify the effects of osteotomy and cartilage procedures on the clinical outcomes of MAT. We could not draw conclusions about the differences in complication, reoperation, survivorship, and failure

No pooled data for complications, reoperation or survival. Studies showed varying outcomes for survivorship and failure rates.	rates between the 2 groups because we did not obtain sufficient data."
Barber-Westin 2017[249] To determine sports activities achieved after meniscus transplantation and if associations exist between sports activity levels and transplant failure or progression of tibiofemoral osteoarthritis (OA).	
Mean follow-up 5.0 (SD 3.7 years); was less than 5 years in 69% of the studies. A quantitative analysis was not undertaken	"It appeared that the majority of individuals returned to low-impact athletic activities after meniscus transplantation. The short-term follow-up did not allow for an analysis on the effect of return to high-impact activities on transplant failure rates or progression of OA."
Bin et al 2017[250] The hypothesis is that the survival rates are similar between medial and lateral MAT but that the clinical outcomes of lateral MAT are better than those of medial MAT at final follow-up.	
Mean follow-up of studies not reported but all had to be at least 5 years 5-10 year survival rates: medial, 97/113; lateral, 108/121 (4 studies, OR 0.71; 95% CI, 0.31-1.64; P = 0.42), I^2 0% >10 years survival rates: medial, 303/576; lateral, 456/805 (8 studies, OR 0.78; 95% CI, 0.52-1.17; P = 0.22), I^2 44% Lysholm score, 3 studies, MD -7.05 (95% CI -10.17, -3.94), I^2 64%, favours lateral. Subgroups by preservation technique (cryo, fresh-frozen, fresh) and fixation (bone plug, soft tissue suture) reported but not extracted.	"Meta-analysis indicated that 85.8% of medial and 89.2% of lateral meniscal allograft transplants survive at midterm (5-10 years) while 52.6% of medial and 56.6% of lateral meniscal allograft transplants survive long term (.10 years). Patients undergoing lateral meniscal allograft transplantation demonstrated greater pain relief and functional improvement than patients undergoing medial meniscal allograft transplantations."
Jauregui et al 2017[251] To assess the overall outcome of MAT and compare the results of different meniscal root fixation techniques	
mean follow-up of 60 (range, 25-168) months Tear rate 9% (95% CI 6.3, 12.2) Failure rate 12.6%. (95% CI 9.1, 16.6) Lysholm scores improved from 57.8 (range 35-72) pre-operatively to 81.4 (range 61-92) post-operatively; SMD 1.5 (95% CI 1.3, 1.8), P<0.001	"This meta-analysis demonstrated significant improvements in clinical outcomes for MAT patients with low tear and failure rates. The data do not demonstrate a difference between soft tissue suture and bone fixation for MAT root fixation. This suggests

	that the technique of root fixation may not have an appreciable influence on clinical outcome, pain reduction, extrusion, or MAT longevity. Further prospective trials are needed."
Lee et al 2017[252] To determine the time to and rate of the return to sports (RTS) after meniscal surgery and to compare these values among the different types of meniscal surgeries. Includes meniscectomy, meniscal repair, and MAT.	
Mean follow-up not reported (reported for individual studies) No quantitative analysis of the 4 MAT studies were reported. After MAT, 67% to 85.7% of athletes returned to sports, and the time to RTS ranged from 7.6 to 16.5 months.	"The time to RTS was shorter, and the RTS rate was higher after meniscal repair than after MAT. Concurrent procedures such as ACLR prolonged the time to RTS, but it had no effect on the RTS rate and the level of sports activity at the time of RTS."
De Bruycker and colleagues in 2017 Aim: To examine the mid and long-term survival of MATs, and to identify prognostic factors.	
65 studies included with 3157 MATs. Studies with less than two years follow-up excluded. Durations were divided into < 3 years, 3-6 years and >6 years. The mean time to MAT was 10 years. The published data was described as being of low methodological quality.	Improvements in Lysholm, IKDC, VAS pain and KOOS scores were found at follow-up (mean 5.4 years, range 2 months to 25 years, which doesn't fit with the exclusion criterion of < 2 years), with a mean allograft survival of 80.9%. Arthroscopic and radiological follow-up found progression of OA by one grade, suggesting a delay in progression of osteoarthritis of 10.5 years, but a lack of complete chondroprotection.

Appendix 4: Retrospective studies in MAT

MAT + OA combined – retrospective studies

Reference	Aim	Population	Study details	Key results (from abstract)
Getgood 2015.[310]	To review a consecutive series of combined MAT and OCA procedures and perform a survivorship analysis in order to better understand the clinical outcome of this rare procedure.	Concomitant MAT and OCA were performed in patients with a combined osteochondral defect of the femoral condyle or tibial plateau (or both) and meniscus deficiency resulting in pain and loss of function. 1983-2011.	Sample size: 48 Follow-up: 6.8 years (range 1.7–17.1). Data collection: Not reported	54.2% required reoperation, but only 22.9% failed (10 MAT and 11 OCA). Mean time to failure: 3.2 years (95% CI 1.5–4.9) and 2.7 years (95% CI 1.3–4.2) for MAT and OCA, respectively. 5-year survivorship was 78% and 73% for MAT and OCA respectively, and 69% and 68% at 10 years. Of those with grafts still intact, statistically significant improvements in all outcome scores were noted.

MAT at the time of meniscectomy

Reference	Aim	Population	Study details	Key results (from abstract)
Li 2017.[291]	To compare the mid-term clinical outcomes of MAT and meniscectomy.	Normal or correctable alignment of joints (≤ ± 3˚), <50 years old, favourable or intraoperatively corrected joint stability, no joint degeneration or extensive damage of articular cartilage. 2006 - 2010	Sample size: 46 (MAT 20; meniscectomy 22) Follow-up: MAT 60.3 ± 21.3 months; meniscectomy 56.5 ± 19.7 months	No results of relevance in abstract. The IKDC, Lysholm and Tegner scores improved in both groups and did not differ significantly between the two groups.

			Data collection: not reported	
MAT post meniscectomy				
Ahn 2016 [224]	To identify risk factors that predict radiographic progression of osteoarthritis after MAT.	Consecutive patients who underwent medial or lateral MATs from 2005 to 2012 by one surgeon, minimum 3 year follow-up. Indication: knee pain despite 6 months of conservative treatment after subtotal or total meniscectomy.	Sample size: 69 Follow-up: 56.2 (range 36 to 102) months Data collection: medical records	A significant risk factor for radiographic progression of osteoarthritis after MAT was medial MAT compared with lateral MAT. Medial MAT compared with lateral MAT was also a significant risk factor (adjusted odds ratio, 3.763; 95% confidence interval, 1.212-11.683).
Alentorn-Geli 2011.[311]	To describe an arthroscopic MAT without bone plugs technique and to report the preliminary results	People receiving MAT between 2001 and 2006, excluding those with ipsilateral knee ligament reconstruction or cartilage repair surgery before MAT or other knee surgeries after MAT	Sample size: 35 (of 59 transplants) Follow-up: 38.6 (13-60) months Data collection: NR	Two graft failures out of 59 transplants (3.4%). Significant improvements for Lysholm, Subjective IKDC Form, and VAS for pain scores were found (P<0.0001).
Felix 2003.[312]	Reviews current status of MAT and presents results of MATs carried out by the authors.	People receiving MAT between 1993 and 1999. Indications included pain and swelling, and less frequently, complaints of mechanical symptoms and instability.	Sample size: 33 Follow-up: 62 months (2.5-8.5 years) Data collection: NR	No abstract. States 83% survival rate, with failure of six menisci.
Faivre 2014.[313]	The hypothesis was that the arthroscopic technique with trans-tibial bony fixation produced better medium-	Consecutive patients who underwent MAT between 2001 and 2010, either as open or arthroscopic procedures (study compares groups)	Sample size: 23	The overall failure rate was 17.4% (4/23, two cases each of complete and partial graft removal). IKDC and KOOS values

	term functional outcomes and minimised allograft extrusion		Follow-up: 63.3 months (range 22-122) Data collection: not reported	were not significantly different between the two groups.
Ha 2010.[314]	To (1) evaluate clinical results after MAT, (2) assess meniscal extrusion after MAT, and (3) investigate the correlation between clinical results and meniscal extrusion.	People undergoing MAT (2002 – 2007) who were available for follow-up.	Sample size: 36 Follow-up: 31.4 months (24-36) Data collection: NR	Lysholm knee score increased (mean, 88.2; range, 70-100) versus preoperative value (mean, 61.2; range, 26-83; P<0.001).
Ha 2011.[315]	To determine clinical, radiologic, and arthroscopic results of our MAT by use of modified bone plug technique, which permits easy passage of the allograft by reducing the size of the posterior bone plug.	Consecutive patients who underwent MAT with the modified bone plug method between 2004 – 2008. Indications: aged 20 – 45 years, active lifestyle, acceptable limb alignment, persistent pain for more than 6 months after meniscectomy.	Sample size: 22 Follow-up: 24.9 months Data collection: not reported	Lysholm score improved significantly, from 68.2 to 89.7 (P=0.002). IKDC subjective knee score improved significantly, from 60.3 to 85.4 (P =0.003). Cartilage degeneration was advanced in 36.4% on second look arthoscopy.
Ha 2014.[316]	To assess the clinical and radiologic outcomes of MAT with serial evaluation at 1 year and at 4 years	Patients who underwent MAT 2006-2009 and underwent clinical and radiologic examinations approximately 1 year after surgery. MAT was performed in patients who had moderate to severe pain after total or subtotal meniscectomy with a 12-month interval from meniscectomy to MAT on the medial side and a 6-month interval on the lateral side.	Sample size: 39 Follow-up: 50.4 months (range 48 to 72) Data collection: not reported	Lysholm knee score increased to median 88 (range, 76 to 100) from preoperative median 79 (range, 37 to 99), which was statistically significant. 54% showed no arthrosis progression and the overall status of arthrosis on anteroposterior radiographs was significantly changed (P < 0.001)

Hommen 2007.[317]	To determine the long-term follow-up results (≥10 years) of 22 consecutive, cryopreserved meniscus allografts.	Those undergoing MAT in a single centre between 1991 and 1995. Indications were prior meniscectomy, <50 years, moderate to severe tibiofemoral pain, mild to advanced arthrosis, and 2 mm of tibiofemoral joint space or greater on 45° weight-bearing posteroanterior radiographs. Patients with surgically correctable malalignment or ligament instability were also candidates.	Sample size: 22 Follow-up: 141 (range 115 – 167 months) Data collection: not reported	25% of medial allografts and 50% of lateral allografts failed. The combined failure rate was 35%. There was a 90% improvement in Lysholm scores, as well as pain scores. There were no discernible Lysholm or pain score differences for both lateral and medial allografts. Eighty-five percent of patients underwent subsequent procedures, 5 of whom required total allograft resection and 2 of whom required partial allograft resection. One allograft required repair.
Jang 2011.[318] Likely overlap patients with Ha 2010	To evaluate the amount of extrusion and clinical and radiographic outcomes of MAT after use of a modified Pollard method to measure the size of the meniscus.	Those having had preoperative allograft sizing by Pollard method (2002-2006), and those having had the size measured by a modified method, reducing the total size of the graft by 5% from the Pollard method (2006-2008).	Sample size 36 Follow-up: 31.4 months (24-36) Data collection: NR	Mean Lysholm knee score increased in all patients, but there was no significant difference between the 2 groups.
Jeon 2015.[319]	To determine whether concomitant excision of a peripheral osteophyte in the tibial plateau with MAT affects allograft extrusion and clinical outcomes.	Those receiving MAT at a single institution who had a peripheral osteophyte in their tibial plateau, 2004 - 2012. Indications included a previous subtotal or total meniscectomy followed by persistent swelling and pain in the involved compartment during activities of daily living.	Sample size: 88 Follow-up: not reported (analysis at 2-years) Data collection: review of records	There were no significant differences in the clinical outcomes (modified Lysholm or Hospital of Special Surgery scores) at 2-year follow-up (<0.762 and <0.298, respectively).
Kazi 2015.[320]	To assess survivorship of meniscal allografts and the benefit of concomitant osteotomy.	People who had MAT +/- osteotomy for previous meniscal injury resulting in subtotal meniscectomy elsewhere or young active patients with uni-compartmental degeneration limiting	Sample size: 85 (86 allografts) Follow-up: 180 months (33-301)	71% remain in situ with adequate function 17% required arthroscopy and meniscal debridement (mean 68 months)

		activities of daily living due to debilitating pain (1990 – 2010). Primary diagnosis was degeneration after previous meniscal injury (medial 43, lateral 41).	Data collection: Database.	28% required total knee arthroplasty (mean 149 months)
Kim 2017[321]	To evaluate the change in meniscal extrusion in both the coronal and sagittal planes after lateral MAT through the midterm follow-up period	Patients who underwent lateral MAT using keyhole technique 2004 – 2012, 36 months follow-up, MRI at 6-weeks, 1-year, and midterm (3-5 years).	Sample size: 46 Follow-up: 51.1 (SD 7.1) months Data collection: not reported	Mean preoperative Lysholm score was 58.9 (SD 8.3) which increased to 90.5 (SD 10.1) at final follow-up, P<0.05.
Koh 2012.[322]	1) to compare medial and lateral MAT with respect to early clinical results; 2) to compare medial and lateral sides with respect to allograft extrusion by MRI; and 3) to explore the possibility of a correlation between extrusion and the clinical outcome.	Those undergoing MAT by a single surgeon (2005 – 2008)	Sample size: 99 Follow-up: 32 (24-59) months Data collection: Records	Mean Lysholm scores increased to 86.6 (33 to 99) from 49.0 (10 to 83) pre-operatively for lateral menisci (p = 0.001) Mean Lysholm scores increased to to 88.3 (32 to 100) from 50.9 (15 to 88) for medial menisci (p < 0.001).
Lee 2017.[290]	Hypothesis: MAT should provide clinical benefits in knees with high-grade cartilage damage, but their graft survivorship should be inferior to that in knees with low-grade chondral degeneration after MAT	Consecutive patients who underwent MAT 2008-2013. Physically active patients with persistent localized knee pain or discomfort after prior subtotal or total meniscectomy were eligible; also patients with mild symptoms if noteworthy chondral wear was observed	Sample size: 222 Follow-up: mean 44.6 (SD 19.7) months Data collection: records and database	Mean (SD) Lysholm score significantly improved from 63.1 (15.1) preoperatively to 85.1 (14.3) On second-look arthroscopic surgery of a mean 19.3 (20.7) months, 11.3% failed MAT procedures (4 medial, 21 lateral); of these, 2.3% lateral MAT procedures went on to allograft removal.

Roumazeille 2015.[323] And Hardy 2013.[324]	To assess graft healing after arthroscopic MAT without bone plugs	All patients who underwent arthroscopic MAT (2005 – 2010) in a single institution. Indications were pain and/or functional sequellae; due to previous total or subtotal meniscectomy; in young patients (≤45 years old).	Sample size: 22 Follow-up: 4.4 (±1.6) years Data collection: NR	At final follow-up, all functional scores had significantly improved. From abstract: At last follow-up, the mean KOOS score was significantly improved: Pain from 50.2 (21.7) to 74.3 (18.2) (p=0.001); Symptoms from 51 (20) to 64.3 (16.7) (p=0.046); Daily Life' from 62.4 (24) to 83 (19.6) (p=0.0005); Activities from 30.3 (26.4) to 48.1 (24.8) (p=0.03); Quality of Life from 27.2 (22.1) to 42 (20.1) (p=0.046). The mean IKDC subjective score was 48.1 (16.1) preoperatively and 60.5 (17.4) at last follow-up (p=0.02).
Ryu 2002.[325]	To examine the potential benefits of meniscal allograft replacement on relieving pain and restoring function.	People undergoing MAT during 1993 – 1999. Indications not reported, primary symptoms of pain or instability at study onset.	Sample size: 25 (26 transplants) Follow-up: 33 (min 12) months Data collection: clinical review (23 clinic, 3 telephone = 26?)	Pain was significantly reduced and function was improved (P <0.001). IKDC scores for activity were reported as normal or nearly normal in 17 and abnormal in 8 participants. Ten second-look procedures revealed 5 normal menisci, 3 with shrinkage, and 2 with recurrent tears.
Sekiya 2003.[326]	To determine the objective and subjective clinical outcomes after combined anterior cruciate ligament reconstruction and MAT.	Those who underwent concomitant MAT and ACL reconstruction between 1994 and 1998 at a single centre and located for follow-up.	Sample size: 28 Follow-up: 2.8 (range 1.8 – 5.6) years	IKDC overall assessment, 86% had normal or nearly normal scores. SF-36 higher than age- and sex matched populations.

			Data collection: Database (incomplete for some data)	
Sekiya 2006.[327]	To determine the clinical outcomes following isolated lateral MAT	Those who underwent isolated lateral MAT between 1993 and 1998 and could be located for follow-up.	Sample size: 25 Follow-up: 3.3 (range 2 – 6) years Data collection: NR	96% believed overall function and activity level were improved after surgery. SF-36 physical and mental component scores were higher than age- and sex matched populations.
Stollsteimer 2000.[328]	Our report looks at both subjective and objective results in a series of meniscal allografts followed-up at regular intervals from 1991 to 1997	Series of people undergoing MAT between 1991 – 1995. Indication: persistent knee pain in the compartment where meniscus had previously been removed.	Sample size: 22 (23 transplants) Follow-up: 40 (range 13 to 69) months Data collection: not reported	Clinical results showed improvement of preoperative pain in all patients.
Vundelinckx 2010.[329]	To evaluate the medium-term results of arthroscopically assisted MAT.	Patients operated on for MAT more than 5 years prior to the study were selected.	Sample size: 34 Follow-up: 8 years and 9 months (range, 62-169 months) Data collection: NR	5 (of 49 who received MAT) received total knee replacement and were considered failures. There was a significant (P<0.001) preoperative mean score to postoperative mean score: decrease in the VAS (7 to 3.4) increase in KOOS (35.8 to 60.2) increase in Lysholm (39.7 to 71.8)

				increase in total SF-36 (51.5 to 75.2) These improvements stayed consistent during the follow-up period. There was no increase in Tegner activity level (P =0.604)
Vundelinckx 2014.[330]	To report the long-term results of a patient cohort whose medium-term results have been reported and to evaluate whether the results are maintained in the long term or deteriorate after a certain period.	MAT performed as an isolated procedure, first published in 2010.	Sample size: 30 Follow-up: mean 152 months (range 112-216). Data collection: database	KOOS and all KOOS subscales, Lysholm, and SF–36 all showed a statistically significant improvement at estimated follow-up periods of 7.5 and 12.5 years compared with preoperative scores. Tegner activity level score remained unchanged during the entire follow-up period
Waterman 2016.[331]	To determine the survivorship, complication rates, and functional outcomes of MAT in an active military population	All military patients undergoing MAT between 2007 and 2013. Surgical indications included only patients with prior total or subtotal meniscectomy and chronic concordant joint line symptoms (eg, pain, mechanical sensation, recurrent effusions).	Sample size: 227 (230 transplants) Follow-up: 2.14 years Data collection: database	4.4% required secondary meniscal debridement, 0.4% required revision MAT and 0.9% underwent TKA. 22% underwent knee-related military discharge. Complications occurred in 21.1% patients, including a secondary tear or extrusion (9%).
Yoldas 2003.[332]	Examined clinical and patient-reported outcomes following MAT with and without combined ACL reconstruction	A select group with complaints of pain and/or instability transplanted between 1993 and 1996. Indications included pain, age and status of articular cartilage, joint stability, and mechanical alignment. “Younger” individuals who had prior meniscectomies with joint line pain during activities of daily living and/or	Sample size: 31 Follow-up: 2.9 years (range 2-5.5) Data collection: NR	Activities of Daily Living score was 86±11 Sports Activities Scale scores was 78±16 Average Lysholm score was 84±14. SF-36 scores indicated that patients were functioning at a level similar to the age- and sex-matched population.

		sports were considered candidates for this procedure		22 stated they were greatly improved, 8 were somewhat improved, 1 was without change.
Yoon 2014.[333]	We compared and analyzed the clinical results of lateral MAT and medial MAT.	Patients who underwent MAT between 2000 and 2010 at a single university hospital	Sample size: 91 Follow-up: 40 months (range 24-125) Data collection: NR	The mean results for ROM, VAS score, IKDC subjective score, Lysholm score, Tegner activity score, and patient subjective satisfaction were not statistically different between the lateral and medial groups (P>0.05). The VAS and Lysholm scores of the isolated group were significantly better than those of the combined group.
Yoon 2014.[334]	To compare the clinical results of MAT after total meniscectomy in torn discoid lateral meniscus and nondiscoid lateral meniscus.	Those receiving lateral MAT at a single institution, 2000 – 2010. Indication: <45 years with pain after subtotal/total meniscectomy and normal alignment	Sample size: 36 Follow-up: 32 months, range 24 to 88 Data collection: not reported	The mean last follow-up IKDC subjective score, Lysholm score, and Tegner activity score of the patient were not significantly different between the discoid group and the nondiscoid group.
Zaffagnini 2016.[335]	To investigate the possibility for return to sport in a large case series of physically active patients who underwent MAT. The secondary aim was to report their midterm clinical outcomes and investigate the factors that could affect these outcomes	Patients who were participating in sport activity (excluding cycling or swimming) before the onset of symptoms related to the meniscus who underwent arthroscopic MAT without bone plugs and had a minimum of 2 years of follow-up at a single institution, no limits regarding age or concomitant procedures, 2006 – 2013.	Sample size: 89 Follow-up: 4.2 (1.9) years Data collection: database and interview	Total KOOS improved from 39.5 (18.5) preoperatively to 84.7 (14.8) at the latest follow-up (P<0.001). Tegner score improved significantly from a median of 2 (IQR, 1-4) preoperatively to 4 (IQR, 3-6) at the latest follow-up (P<0.001), although it did not reach the preinjury level of 6 (IQR, 5-7) (P<0.001). 74% were able to return to sport after 8.6 (4.1) months. 49% returned to the same level as preinjury. 12% underwent a surgical procedure during the follow-up period.

Zaffagnini 2016.[336] Likely overlap with participants in Zaffragnini 2016[335]	To report the survivorship, based on different failure criteria, of a large single-centre cohort of consecutive patients, treated with arthroscopic bone plug free meniscus transplantation technique, associated with required surgery in almost 50 % of cases. The secondary aim was to report the midterm clinical outcomes and investigate variables that could potentially influence them.	All receiving MAT at a single institution between 2004 – 2013. Minimum 2 years follow-up with no limits regarding age or concomitant procedures.	Sample size: 147 Follow-up: 40 (1.9) years Data collection: database and interview	There was a significant ($p < 0.05$) and clinically relevant decrease in the VAS and increase in KOOS and Lysholm from pre-operative mean score to post-operative mean score. 5% experienced surgical failure. The mean overall survival time was 9.7 years (CI 9.1–10.3). As 11% presented poor Lysholm scores, 16% in total were considered clinical failures. The mean overall survival time was 8 years (CI 7.1–8.8).

ACLR: anterior cruciate ligament reconstruction; HSS: Hospital for Special Surgery; KOOS: knee injury and osteoarthritis outcome score; MAT: meniscal allograft transplantation; NR: not reported; TKA: total knee arthroplasty

Appendix 5. Suggestion to UK Health Technology Assessment Programme.

23rd July 2018

1. **Intervention:** Imaging of knees every 2 years after meniscectomy, with MRI (or other imaging method if researchers justify that).
2. **Patient group:** people who have had meniscectomy
3. **Setting:** orthopaedic clinics
4. **Control:** not applicable
5. **Study design:** diagnostic cohort study
6. **Outcomes:** identification of the subgroup who will do worst after meniscectomy and who might benefit from early meniscal allograft transplantation (MAT). Secondary outcome if feasible: optimum time to intervene with MAT. This might need a trial, but by identifying when deterioration in articular cartilage starts, it might be possible to hypothesise when to perform MAT.
7. **Minimum duration of follow-up:** 3 years

Background

The meniscal cartilages are fibrocartilaginous structures lying between the femoral condyles and the tibial plateaux. They have a number of functions including load-bearing and shock absorption in the knee, with the lateral meniscus thought to carry 70% of the load in its compartment, and the medial one 50%, when the leg is straight. See Hannon et al 2015[218] for review of the history of meniscectomy and of MAT.

Meniscectomy is regarded as leading to early osteoarthritis because of increased stress on articular cartilage. The articular cartilage under the menisci is thinner than on other parts of the tibial plateau (Verdonk 2016 [220]) and so the submeniscal region is more at risk of OA if the meniscus is removed. Because meniscal injuries often occur in sport, those afflicted are often young. For example in the case series of 63 patients reported by Cameron and Saha[221], the average age at meniscectomy was 24. An even younger cohort was reported by Pengas et al[337] (from the Dundee series of Smillie from the 1960s and 1970s) in which 313 patients with mean age 16 (range 10-19) at meniscectomy were followed up for about 40 years (mean age at assessment 57, range 43-67). OA was found in 87% of meniscectomised knees but in only 18% of non-operated knees. All were either symptomatic (KOOS 70) or (13%) had had knee replacement. Hannon et al conclude that "total meniscectomy is a poor treatment modality".

Acute meniscal injuries due to trauma in young people should be distinguished from the degenerative meniscal lesions that are common in older people – 25% in age range 50-59 years increasing to 45% in those aged 70-79 (ESSKA consensus[338]. The ESSKA consensus was that meniscectomy should not be a first line treatment in degenerative meniscal lesions.

Several authors have reported that meniscectomy leads to OA[231, 256, 311, 339] but the evidence is mixed for several reasons. One is duration of follow-up. Jackson[238] reviewed 577 knees after meniscectomy

and compared them with the patients' other knees. Definite generative changes on Xray (such as joint space narrowing, formation of osteophytes, and sclerosis) were much more common in meniscectomised knees (21% versus 5%) but took time to develop, being seen in 22% (control knees 4%) at under 20 years, 53% at 20-29 years (controls 13%) and 67% at 30-40 years (controls nil). However only about half of those with radiological degeneration had painful knees.
So many people have good results for many years after meniscectomy. However clinical consensus is that there is a subgroup of patients, perhaps 10%, who do particularly badly after meniscectomy, developing early severe OA. These are the people who have most to gain by MAT.

It has been suggested that prophylactic MAT be done at the time of meniscectomy and there is one small study in which a proportion of patients had immediate MAT. This study is too small and with duration of follow-up too short, to provide an answer. The consensus is that at present, prophylactic MAT is not indicated. The IMREF consensus[219] statement recommended three main indications for MAT;

- Unicompartmental pain following total or defunctioning subtotal meniscectomy
- As a concomitant procedure to ACL reconstruction in order to prolong the life of ACL reconstruction
- As a concomitant procedure to articular cartilage repair in a meniscus-deficient compartment

However, the IMREF consensus recommended that MAT was not indicated in patients with no meniscus but no symptoms. This could be seen as a problem given that people may be developing OA without symptoms in the early stages. The decision was based on a paucity of evidence of chondroprotective benefit in asymptomatic people, and consideration of the significant re-operation rate after MAT (as high as 35%). However the consensus did extend "symptomatic" to patients with radiological signs of OA in the absence of symptoms.

Research questions

The main problem is that we cannot at present identify the subgroup who are going to do badly and develop OA soon after meniscectomy. The research question is therefore whether we can identify them before they get advanced OA, intervene early with MAT, and prevent or at least delay OA.

There are two (at least) related questions which are particularly relevant if we can identify the subgroup that will do worst and intervene with early MAT. The first question is the extent to which MAT prevents or delays OA. This probably needs an RCT. Patients in the subgroup who get MAT could continue to have MRI and clinical follow up to determine outcomes.

The second question concerns repeat MAT. The allografts may deteriorate over time, disintegrate and be removed. Repeat MAT with a new allograft seems logical, but this is not standard practice. There may therefore be a case for a trial of repeat MAT versus debridement and conservative care till patients reach knee replacement age.

Methods

The exact methods could be defined by applicants if the topic was advertised, but we make some suggestions.

Our view is that a cohort study with annual imaging would be required. Imaging could follow the protocol developed by the National Institutes of Health Osteoarthritis Initiative[340] (imaged at 3T with

volume acquisitions etc) followed by modern image analysis, to detect differences in rate of change between groups. Bowes et al[341] have shown that they can identify significant differences even using very small numbers (as low as six in one study).

See also Guermazi[342] and Crema[343].

It is possible to identify change at one year follow up.

Patients would be followed up clinically until a pre-defined endpoint was reached in terms of patient outcomes such as symptom scores (Lysholm, KOOS, IKDC, Tegner) and clinical assessment. One problem may be that those who are rapidly going to develop OA, may have few or no symptoms in the early years, till OA develops. So a situation may arise of MAT being indicated in asymptomatic people, to avoid progression to severe OA.

Imaging would be done before meniscectomy, and then at yearly intervals post-op for as long as deemed necessary. Once the subset of those who are doing badly has been identified, there would be a look-back (by radiologists unaware of the patient outcomes) at the imaging data and other appropriate data to seen whether it would have been possible to predict poor outcome prior to surgery. There are some relatively novel techniques to look for early knee degenerative changes.

The absolute numbers recruited would not need to be very large but would be based on getting an adequate number of patients who do badly, expected to be about 10% of the whole meniscectomy population. There would need to be sufficient people in the poor outcomes subgroup to allow analysis by baseline factors, so if we needed 20 in this group, we would need to recruit 200+ overall. That would need a multi-centre study to recruit in a reasonable time. There has been a trend in recent years to try to preserve menisci or parts thereof when possible.

Some people having meniscectomy have other knee pathology such as articular cartilage damage. The study could recruit only people with no other knee pathology. But since those with other damage will do worse without MAT, they may have more to gain. So paradoxically, MAT may be more cost-effective in the group with other problems. This needs research.