NHS England Evidence Review:

Fresh osteochondral allograft transplantation for osteochondral defects of the knee

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of fresh osteochondral allograft (OCA) transplantation compared to autologous chondrocyte implantation (ACI) with bone graft, ACI alone or no surgical treatment in patients with large (>2cm^2) osteochondral defects of the knee joint in whom best supportive care has failed, irrespective of previous cartilage repair.

Fresh OCA is a surgical technique to treat large osteochondral defects (a focal area of damage that involves both the cartilage and a piece of underlying bone). The grafts are stored at four degrees or above (not frozen) and implanted within 28 days of harvest.

ACI is a two-stage process requiring extraction and growth of chondrocytes from biopsied healthy cartilage and then an operation to implant these cells. In osteochondral defects a bone graft may be carried out prior to the chondrocyte implantation. When a bone graft is not possible ACI can be performed alone. For some patients no surgical treatment is possible until joint deterioration reaches the point of requiring total knee replacement.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with fresh OCA more than others, as well as the criteria used by the included studies to confirm a diagnosis of osteochondral defects and the size of the defects.

2. Executive summary of the review

Nine observational studies were included in the evidence review (Abolghasemian et al 2019, Brown et al 2011, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Raz et al 2014, Sadr et al 2016, and Thomas et al 2013). One study was a prospective case series (Brown et al 2011) and the other eight were retrospective case series. They included between 22 and 135 subjects (between 28 and 149 knees). Causes of osteochondral lesions included trauma, osteochondritis dissecans (OCD) and steroid-associated osteonecrosis. Studies with more than 20 patients were included where it was reported, or seemed very likely, that all or almost all lesions were osteochondral rather than chondral, and that all or almost all lesions exceeded 2cm^2 in area. No studies compared fresh osteochondral allograft (OCA) transplantation to autologous chondrocyte implantation (ACI) with bone graft, ACI alone or no surgical treatment.

Studies reported outcomes at timepoints ranging from six months to 21.8 years after surgery. Seven of the studies were based in the USA and two were based in Canada.

Research Question 1:

1. In people with large osteochondral defects >2cm^2, what is the clinical effectiveness of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?

Critical outcomes

The critical outcomes for decision making are knee specific scores, quality of life (QOL) scores and activities of daily living (ADL) scores.

The certainty of the evidence for all critical outcomes was very low when assessed using modified GRADE.

Knee specific score

Seven case series reported non-comparative evidence for knee specific scores[1] for people with large osteochondral defects who received fresh OCA transplantation. For all the knee scores reported except the International Knee Documentation Committee (IKDC) pain score, a higher score indicates a better outcome.

The prospective case series by Brown et al 2011 (n=34 at baseline, 24 at 2 years) reported knee specific scores (subscales from the Knee injury and Osteoarthritis Outcome Score (**KOOS**)) at baseline, 6 months, 1 year and 2 years. The mean +/- standard deviation (SD)

[1] **Summary of Knee Scores**

Higher score is better for all scores apart from the IKDC pain subscore, for which higher score is worse.

- IKDC (International Knee Documentation Committee): The full IKDC includes 10 questions measuring symptoms, including pain (6 questions), sports activities (3 questions), ADL (1 question).
- KS (Knee Society Score): symptoms (3 items) (including pain (2 items)), functional activities (3 items - use of aids, standing, walking), standard activities (6 items), advanced activities (5 items), knee-related activities (3 items).
- KOOS (Knee injury and Osteoarthritis Outcome Score): symptoms (5 items), stiffness (2 items), pain (9 items), sports/ recreation (5 items), each rated on a 5-point scale.
- MAPS (modified Merle d'Aubigné-Postel): measures pain, gait and mobility, each on a 6-point scale. Minimum score 3, maximum score 18.
- mHSS (modified Hospital for Special Surgery) score reports: Pain intensity (5-point scale); Instability (3-point scale); Use of walking aids; Walking distance; Knee extension; Knee flexion; Effusion. Maximum score 100.
- WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index): pain (5 items), stiffness (2 items), each rated on a scale 0-4, max score 96.

scores at these time points (with p values comparing baseline vs 2 years) for pain were 59 +/-17; 79 +/-17; 77 +/-18; 74 +/-22; p=0.028; for symptoms were 58 +/-16; 69 +/-20; 69 +/-21; 70 +/-20; p=0.172; and for sports were 37 +/-26; 65 +/-27; 59 +/-23; 57 +/-30; p=0.005. The scores for pain and sports showed statistically significant improvements between baseline and 2 years, while the improvement in the symptoms score was not statistically significant. The score improvements for pain at 6 months and 1 year, and for sport at 6 months exceeded the minimum clinically important difference (MCID) defined in the PICO, but declined thereafter[2].

Cotter et al 2018 (n=36 patients, 38 knees) reported the **KOOS** scores at mean 7.29 +/-3.30 years follow-up and found mean improvements in score between pre-op and latest follow-up of 20.8 (pain), 14.8 (symptoms) and 25.96 (sport) (all p<0.001). The score improvements for pain and sport exceeded the MCID defined in the PICO. The study authors reported that the improvement in symptoms score exceeded the MCID but did not provide the MCID definition.

Four case series reported **IKDC total** score and all found statistically significant improvements. Brown et al 2011 (n=34 at baseline, 24 at 2 years) reported mean +/- SD scores at baseline of 45 +/-11, 6 months of 57 +/-14, 1 year of 59 +/-15 and 2 years of 62 +/-20; p<0.001 (comparing baseline vs 2 years). Cotter et al 2018 (n=36 patients, 38 knees) found a mean improvement at mean 7.29 +/- 3.30 years follow-up of 25.54 (p<0.0001). The study authors reported that the improvement exceeded the MCID but did not provide the MCID definition. Gracitelli et al 2017 (n=29 knees) found a mean pre-op score of 32.9 and mean score at follow-up (median 6.6 years, range 2 to 23.6 years) of 54.3 (p=0.012). Sadr et al 2016 (n=137 knees) found a mean (+/- SD) pre-op score of 44.2 +/- 17.5 and mean score at follow-up (median 6.3 years, range 1.9 to 16.8 years) of 82.3 +/- 15.8 (p<0.001).

Four case series reported **IKDC pain** score and all but one reported statistically significant improvements (for this score a higher score indicated a worse outcome). Early et al 2018 (n=23 knees) found a mean pre-op score of 7.2 and mean follow-up score of 2.8 (p<0.001), with mean follow-up 11.0 years (range 2.9 to 29 years). Gortz et al (n=22 knees) found a mean pre-op score of 7.1 and mean follow-up score of 2.0 (p<0.001), with mean follow-up 67 months (range 25 to 235 months). Gracitelli et al 2017 (n=29 knees) found a mean pre-op score of 6.4 and mean follow-up score of 4.5 (p=0.055), with median follow-up 6.6 years, range 2 to 23.6 years. Sadr et al 2016 (n=137 knees) found a mean (+/- SD) pre-op score of 5.3 +/- 2.5 and follow-up score of 2.1 +/- 2.2 (p< 0.001), with median 6.3 years, range 1.9 to 16.8 years follow-up.

Four case series reported **IKDC function** score and all reported statistically significant improvements. Early et al 2018 (n=23 knees) found a mean pre-op score of 3.3 and mean follow-up score of 6.5 (p=0.005) at mean 11.0 years (range 2.9 to 29 years) follow-up. Gortz et al 2010 (n=22 knees) found a mean pre-op score of 3.5 and mean follow-up score of 8.3 (p=0.002) with mean follow-up 67 months (range 25 to 235 months). Gracitelli et al 2017 (n=29 knees) found a mean pre-op score of 2.8 and mean follow-up score of 6.0 (p=0.001) at median 6.6 years (range 2 to 23.6 years) follow-up. Sadr et al 2016 (n=137 knees) found a mean (+/- SD) pre-op score of 3.5 +/- 1.8 and follow-up score of 8.1 +/- 2.0 (p<0.001), at median 6.3 years (range 1.9 to 16.8 years) follow-up.

[2] MCIDs defined in the PICO were: 16.7 for KOOS pain and 25 for KOOS sports/recreation before and after OCA

Three case series reported the **Knee Society-function** score and all reported statistically significant improvements. Early et al 2018 (n=23 knees) found a mean pre-op score of 61.7 and mean follow-up score of 87.5 (p=0.0030) at mean 11.0 years (range 2.9 to 29 years) follow-up. Gortz et al 2010 (n=unclear) found a mean pre-op score of 60.0 and mean follow-up score of 85.7 (p=0.005) at mean 67 months (range 25 to 235 months) follow-up. Sadr et al 2016 (n=137 knees) found a mean (+/- SD) pre-op score of 72.3 +/- 18.6 and follow-up score of 95.7 +/- 9.6 (p<0.001) at median 6.3 years (range 1.9 to 16.8 years) follow-up.

One case series (Sadr et al 2016) (n=137 knees) reported the **Knee Society-knee** score with a mean (+/- SD) pre-op score of 81.1 +/- 14.8 and mean follow-up score of 94.3 +/- 8.8 (p<0.001) at median 6.3 years (range 1.9 to 16.8 years) follow-up, a statistically significant improvement.

One case series (Cotter et al 2018) (n=36 patients, 38 knees) reported a statistically significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index **(WOMAC) pain** score and **WOMAC stiffness** score (both p<0.0001) at mean 7.29 +/- 3.30 years follow-up; actual scores or change in scores were not reported. The study authors reported that the improvement in both scores did not exceed the MCID but did not provide the MCID definition.

Two case series reported the **modified Merle d'Aubigné-Postel** scores and both reported statistically significant improvements. Gortz et al 2010 (n=25 knees) found a mean pre-op score of 11.3 and mean follow-up score of 15.8 (p<0.001) at mean 67 months (range 25 to 235 months) follow-up. Sadr et al 2016 (n=137 knees) found a mean (+/- SD) pre-op score of 13.6 +/- 2.0 and mean follow-up score of 16.8 +/- 1.5 (p< 0.001) at median 6.3 years (range 1.9 to 16.8 years) follow-up.

One case series (Abolghasemian et al 2019) (n=60 knees) reported the **modified Hospital for Special Surgery** score and found a mean pre-op score of 69 (range 48 to 85) and mean follow-up score of 85.5 (range 56 to 100), p < 0.001 at mean 15.5 years (range 4.3 to 31.7) years follow-up.

Quality of life scores

Two case series (one prospective and one retrospective) reported QOL scores[3]. For the KOOS QOL score, Brown et al 2011 (n=34 at baseline, 24 at 2 years) reported a mean +/- SD score at baseline of 23 +/-17, at 6 months of 47 +/-21, at 1 year of 49 +/-24, and at 2 years of 48 +/-22 (statistical test only reported between baseline vs 2 years; p<0.001, a statistically significant improvement). Cotter et al 2018 (n=38 knees, 36 patients) reported a statistically significant improvement in mean KOOS QOL score of 20.88 (p<0.0001) at mean 7.29 +/- 3.30 years follow-up but actual scores were not reported. The study authors reported that the improvement in QOL score exceeded the MCID but did not provide the MCID definition. Cotter et al 2018 (n=38 knees, 36 patients) also reported the SF12-mental and SF12-physical scores. They found a statistically significant improvement in the SF12-physical score (p=0.002) but no statistically significant change in the SF12-mental score (p=0.910); actual scores and changes in scores were not reported.

[3] **Summary of QOL scores**
Higher score is better for all scores

- SF12: 12 questions taken from the SF-36 Health Survey which are combined and weighted to report on mental and physical functioning subscales.
- KOOS QOL: 4 items on knee-related QOL: being aware of your knee, difficulty with your knee, lack of confidence in your knee, lifestyle modifications because of your knee.

Activities of daily living

Two case series (one prospective and one retrospective) reported ADL subscores[4] from two knee specific scores. For the **KOOS ADL** score, Brown et al 2011 (n=34 at baseline, 24 at 2 years) reported a mean +/- SD score at baseline of 69 +/-21, at 6 months of 85 +/-16, at 1 year of 84 +/-16, and at 2 years of 83 +/-23 (statistical test only reported between baseline vs 2 years; p=0.58, not statistically significant). Cotter et al 2018 (n=38 knees, 36 patients) reported a statistically significant improvement in score of 20.88 (p<0.0001) at mean 7.29 +/- 3.30 years follow-up but actual scores were not reported. The study authors reported that the improvement in ADL score exceeded the MCID but did not provide the MCID definition. Cotter et al 2018 (n=38 knees, 36 patients) also found a statistically significant improvement in the **WOMAC (function)** score (p<0.0001) but again actual scores and changes in scores were not reported.

Apart from the MCID changes in KOOS scores, the clinical significance of the improvements in all other knee specific, QOL and ADL scores reported was not clear.

Important outcomes

The important outcomes for decision making are allograft survival rate and failure of transplantation.

The certainty of the evidence for all important outcomes was very low when assessed using modified GRADE.

Allograft survival rate

Overall graft survival decreased over time. Six retrospective case series reported **allograft survival rate at five years** (Abolghasemian et al 2019, n (at 5 years) not stated; Cotter et al 2018, n not stated; Early et al 2018, n=33 knees; Gortz et al 2010, n=28 knees; Gracitelli et al 2017, n=39 knees, and Sadr et al 2016, n=149 knees). They found survival rates of 90% (95% confidence interval (CI) 83% to 94%), 97%, 90%, 89%, 82.6% and 95% respectively (CI reported where available).

Five studies reported **allograft survival rate at 10 years** (Abolghasemian et al 2019, n=69; Early et al 2018, n=33 knees; Gracitelli et al 2017, n=39 knees; Raz et al 2014, n=58 knees; Sadr et al 2016, n=149 knees). They found survival rates of 79% (95%CI 70% to 86%), 82%, 69.6%, 91% (95%CI 80% to 96%), and 93% respectively (CI reported where available).

Two studies reported **allograft survival rate at 15 years** (Abolghasemian et al 2019, n not stated; Raz et al 2014, n=58). They found survival rates of 64% (95%CI 53% to 73%) and 84% (95% CI 50% to 81%) respectively.

[4] **Summary of ADL scores**
Higher score is better for all scores

- KOOS ADL: 17 items which cover a range of ADL activities (eg. using stairs, sitting, standing, walking, getting dressed/ undressed, using bath/toilet, shopping, domestic tasks).
- WOMAC function: 17 items which cover a range of ADL activities (eg. using stairs, sitting, standing, walking, getting dressed/ undressed, using bath/toilet, shopping, domestic tasks).

Two studies reported **allograft survival rate at 20 years** (Abolghasemian et al 2019, n=18; Raz et al 2014, n=58). They found survival rates of 47% (95%CI 34% to 59%) and 69% (95%CI 50% to 81%) respectively.

Failure of transplantation

Failure rates were reported in eight retrospective case series at time periods between 46.2 months and 21.8 years after surgery. **Graft failure** in most studies was defined as revision or removal of the graft, and/or conversion to total knee arthroplasty (TKA), but two studies (Gortz et al 2010 and Gracitelli et al 2017) appeared to have more inclusive definitions including the need for other types of surgery. Variations in failure rates across studies did not always appear to correspond with duration of follow-up. The two studies with more comprehensive definitions of failure reported higher failure rates at shorter time intervals.

- At mean 46.2 +/- 13.4 months follow-up Thomas et al 2013 (n=61 knees) reported a failure rate of 9.8%.
- At mean 67 (range 25 to 235) months follow-up Gortz et al 2010 (n=28 knees) reported a failure rate of 18%.
- At median 6.3 (range 1.9 to 16.8) years follow-up Sadr et al 2016 (n=149 knees) reported a failure rate of 8%.
- At median 6.6 (range 2 to 23.6) years follow-up Gracitelli et al 2017 (n=39 knees) reported a failure rate of 26%.
- At mean 7.29 +/- 3.30 years follow-up Cotter et al 2018 (n=39 knees) reported a failure rate of 5.1%.
- At mean 11 (range 2.9 to 29) years follow-up Early et al 2018 (n=33 knees) reported a failure rate of 27%.
- At mean 13.8 (range 1.7 to 34) years follow-up Abolghasemian et al 2019 (n=113 knees) reported a failure rate of 42%.
- At mean 21.8 (range 15 to 42) years follow-up Raz et al 2014 (n=58 knees) reported a failure rate of 22.4%.

Research Question 2

2. In people with large osteochondral defects >2cm^2, what is the safety of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?

Complications relating to the surgery were reported in three retrospective case series, all of which provided very low certainty evidence when assessed using modified GRADE. The time points at which complications were reported were not stated. The three case series (Abolghasemian et al 2019, n=113; Cotter et al 2018, n=37 patients; Thomas et al 2013, n=61) reported total complications rates of 2.7%, 10.3% and 8.2% respectively. The commonest complication was infection with rates of 1.8%, 2.6% and 3.3% respectively.

Research Question 3

3. In people with large osteochondral defects >2cm^2, what is the cost effectiveness of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?

No evidence was identified on the cost effectiveness of fresh OCA compared with ACI with bone graft, ACI alone or no surgical treatment.

Research Question 4

4. From the evidence selected, are there any subgroups of people that may benefit from fresh OCA more than the wider population of interest?

No evidence was identified regarding any subgroups of patients that would benefit more from treatment with fresh OCA.

Eight studies reported that they included subjects who had had at least one previous procedure (Abolghasemian et al 2019, Brown et al 2011, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Sadr et al 2016, and Thomas et al 2013), which included some of the subgroups of interest (for example previous cartilage repair, including microfracture, and meniscal procedures), and seven studies included both adults and children (Brown et al 2011, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Raz et al 2014, and Sadr et al 2016). However, no studies reported any outcomes separately for any of these groups.

Research Question 5

5a. From the evidence selected, what are the criteria used by the research studies to define osteochondral defects?

The criteria used to define osteochondral defects were generally referred to within study inclusion criteria.

Two studies (Early et al 2018, and Gortz et al 2010) of OCA in patients with steroid-associated osteonecrosis stated that they included patients with stage III-IV (modified Ficat/Arlet stage)[5] lesions secondary to steroid-associated necrosis of the femoral condyles. The authors described the lesions as ‘advanced’ but did not provide any details about how this classification was applied to patients with osteonecrosis of the knee.

There were two studies of OCA in patients with OCD. Sadr et al 2016 referred to patients with ‘type III or IV OCD’ in their inclusion criteria, but with no further details of what this meant or how it was applied. Cotter et al 2018 referred to the ICD9 definition of OCD in their inclusion criteria, but with no further details.

One study (Brown et al 2011) stated that they included patients with International Cartilage Repair Society (ICRS) grade 4 lesions[6].

Two studies (Abolghasemian et al 2019, and Raz et al 2014) used osteochondral lesion dimensions (both used >3 cm in diameter, >1 cm in depth) to define the lesions to be included in the study. Abolghasemian et al 2019 stated that lesions were posttraumatic, and

[5] Ficat/ Arlet classification – originally a classification for osteonecrosis of the hip.
[6] ICRS Grade Characteristics
0 Normal; 1 Nearly normal (soft indentation and/or superficial fissures and cracks); 2 Abnormal (lesions extending down to <50% of cartilage depth); 3 Severely abnormal (cartilage defects >50% of cartilage depth); 4 Severely abnormal (through the subchondral bone)

Raz et al 2014 specified that they were posttraumatic or OCD, but there were no further details.

Thomas et al 2013 referred only to 'medium to large osteochondral lesions' and Gracitelli et al 2017 to 'large osteochondral traumatic lesions due to fractures on the knee'. Neither provided further details on how these were defined or identified.

5b. From the evidence selected, what size were the osteochondral defects?

Three studies defined lesion size by area: Thomas et al 2013 (mean lesion size 365mm^2), Cotter et al 2011 (average defect size 460.87+/-168.12 mm^2), and Brown et al 2011 (mean lesion size 5.7 cm^2 (range 1.5-15 cm^2)). Two studies defined the minimum dimensions of the lesion only, which in both were >3 cm in diameter, >1 cm in depth (Abolghasemian et al 2019, and Raz et al 2014). Four studies defined graft area rather than lesion area: Sadr et al 2016 (mean allograft size 7.3 cm^2 (range 2.2-25 cm^2)), Early et al 2018 (mean total allograft surface area 10.6 cm^2 (range 4.0–19.0 cm^2)), Gortz et al 2010 (mean total allograft surface area 10.8 cm^2 (range 5.0–19.0 cm^2)) and Gracitelli et al 2017 (mean total allograft surface area 14.5 cm^2 (range 2–33 cm^2)).

5c. From the evidence selected, were patients who had osteoarthritis included in the studies?

Eight of the studies did not state whether or not any of the included patients had osteoarthritis at the time of inclusion in the study. One study (Brown et al 2011) stated that 23 (64%) of the included subjects had focal osteoarthritic defects (idiopathic and posttraumatic types).

5d. From the evidence selected, were patients who had previous cartilage repair included in the studies?

Seven studies included patients who had had previous cartilage repair, including microfracture (Brown et al 2011, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Sadr et al 2016, Thomas et al 2013). The remaining two studies did not state whether or not patients had had previous cartilage repair (Abolghasemian et al 2019, and Raz et al 2014).

Limitations

There were no comparative studies which considered the clinical effectiveness or safety of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment. Factors relating to the design and conduct of the studies meant that they were at high risk of bias, and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE. Studies reported outcomes at timepoints ranging from six months to 21.8 years after surgery. Only one study (Brown et al 2011) reported the critical outcomes at specific time points between six months and two years.

Study subjects were heterogeneous and limited information was provided about them. Two studies included adults only and the remainder also included subjects aged under 17 years. No studies analysed different age groups separately. The studies used various definitions of osteochondral lesions, or no clear definition, and the size of lesions varied significantly across studies and was described in a variety of ways. In addition, most of the studies had incomplete inclusion of eligible subjects and/or significant loss to follow-up. Most studies appeared to be carried out in a single centre and some included interventions carried out by

a single surgeon, so it is not clear how generalisable their findings might be to other settings. Eight studies reported that subjects had additional procedures at the same time as OCA, which included bone grafts, osteotomy, meniscal allograft and ligament reconstruction. It is not clear to what extent any reported effects may be attributable to the OCA or to these additional procedures.

Conclusion

This review included nine case series which provide very low certainty evidence on critical and important outcomes following fresh OCA for large osteochondral defects. All studies which reported knee specific scores found statistically significant improvements with varying durations of follow-up up to mean 15.5 years, but only two reported improvements which met the MCID threshold defined in the PICO, one at six months and a year (although this improvement was not maintained), and one at a mean of 7.29 years.

The studies identified for this review therefore provide very low certainty evidence that OCA in patients with large osteochondral defects may improve knee specific scores, but there is very little evidence on whether the improvements are clinically significant to patients. It is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of OCA compared with ACI with bone graft, ACI alone or no surgical treatment.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people with large osteochondral defects >2cm^2, what is the clinical effectiveness of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?
2. In people with large osteochondral defects >2cm^2, what is the safety of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?
3. In people with large osteochondral defects >2cm^2, what is the cost effectiveness of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?
4. From the evidence selected, are there any subgroups of people that may benefit from fresh OCA more than the wider population of interest?
5. From the evidence selected,
    a. What are the criteria used by the research studies to define osteochondral defects?
    b. What size were the osteochondral defects?
    c. Were patients who had osteoarthritis included in the studies?
    d. Were patients who had previous cartilage repair included in the studies?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The searches for evidence were informed by the PICO document and were conducted on 6th November 2020.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Nine papers were identified for inclusion (Abolghasemian et al 2019, Brown et al 2011, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Raz et al 2014, Sadr et al 2016, and Thomas et al 2013). Table 1 provides a summary of these included studies and full details are given in Appendix E.

Eight papers reported retrospective case series and one (Brown et al 2011) reported a prospective case series.

No cost effectiveness studies suitable for inclusion in this evidence review were identified.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Abolghasemian et al 2019 Retrospective case series Toronto, Canada	113 patients (113 knees) with posttraumatic osteochondral defect No subgroups reported	**Intervention** Fresh OCA 77 (68%) also had meniscal allograft, 74 (65%) also had realignment osteotomy **Comparison** None	**Critical outcomes** Pre-op and latest follow-up (mean follow-up 15.5 years (range 4.3 to 31.7 years)) • Knee specific score in those with surviving grafts: mHSS score **Important outcomes** • Graft survival at 5, 10, 15 and 20 years • OCA failure at mean follow-up 13.8 years (range 1.7 to 34 years) **Safety** • Complications (timepoint not stated)
Brown et al 2011 Prospective case series Oregon, USA	34 patients (34 knees) with osteochondral defects of the femur No subgroups reported	**Intervention** Fresh OCA Nine (26%) had concurrent procedures (osteotomy, meniscus transplant or ligament reconstruction) **Comparison** None	**Critical outcomes** Reported at baseline, 6 months, 1 year, 2 years • Knee specific score: KOOS pain, symptoms, sports • QOL: KOOS QOL • ADL: KOOS ADL **Important outcomes** • None reported
Cotter et al 2018 Retrospective case series Chicago, USA	37 patients (39 knees) with Osteochondritis Dissecans No subgroups reported	**Intervention** Fresh OCA 11/37 (30%) had concomitant procedures (meniscal allograft or osteotomy)	**Critical Outcomes** Improvement between pre-op and latest follow-up (mean follow-up 7.29 +/- 3.30 years)

		Comparison None	• Knee specific scores: IKDC, KOOS, WOMAC • QOL: SF12 physical and mental, KOOS QOL • ADL: KOOS ADL, WOMAC function **Important outcomes** • Graft survival up to 5 years • OCA failure at mean follow-up 7.29 +/- 3.30 years **Safety** • Complications (timepoint not stated)
Early et al 2018 Retrospective case series California, USA	25 patients (33 knees) with osteochondral defects secondary to steroid-associated osteonecrosis No subgroups reported	**Intervention** Fresh OCA 19/33 (58%) also had bone graft **Comparison** None	**Critical Outcomes** Pre-op and latest follow-up (mean follow-up 11 years (range 2.9 to 29 years)) • Knee specific scores: IKDC, Knee Society function **Important outcomes** • Graft survival at 5 and 10 years • OCA failure at mean follow-up 11 years (range 2.9 to 29 years)
Gortz et al 2010 Retrospective case series California, USA	22 patients (28 knees) with osteochondral defects secondary to steroid-associated osteonecrosis No subgroups reported	**Intervention** Fresh OCA 18/28 (64%) also had bone graft **Comparison** None	**Critical Outcomes** Pre-op and latest follow-up (mean follow-up 67 months; range 25 to 235 months) • Knee specific scores: IKDC, modified Merle d'Aubigné-Postel, Knee Society function **Important outcomes** Reported at mean follow-up 67 months (range 25 to 235 months) • Graft survival • OCA failure
Gracitelli et al 2017 Retrospective case series	39 patients (39 knees) with osteochondral lesions after knee fracture No subgroups reported	**Intervention** Fresh OCA	**Critical Outcomes** Reported at latest follow-up (median follow-up 6.6

California, USA		12/39 (43.6%) had a concomitant meniscal allograft. There were 23 other concomitant procedures (number of knees/patients not stated) **Comparison** None	years (range 2 to 23.6 years)) • Knee specific scores: IKDC, modified Merle d'Aubigné-Postel, Knee Society function **Important outcomes** • Graft survival at 5 and 10 years • OCA failure at latest follow-up
Raz et al 2014 Retrospective case series Toronto, Canada	58 patients (58 knees) with posttraumatic osteochondral defects or Osteochondritis Dissecans No subgroups reported	**Intervention** Fresh OCA 36 (62%) had concomitant osteotomy **Comparison** None	**Critical Outcomes** None reported **Important outcomes** • Graft survival at 10, 15 and 20 years • OCA failure at latest follow-up (mean follow-up 21.8 years (range 15 to 42 years))
Sadr et al 2016 Retrospective case series California, USA	135 patients (149 knees) with Osteochondritis Dissecans No subgroups reported	**Intervention** Fresh OCA Not reported whether any concomitant procedures carried out **Comparison** None	**Critical Outcomes** Pre-op and latest follow-up. Median follow-up 6.3 years (range 1.9 to 16.8 years) • Knee specific score: IKDC, modified Merle d'Aubigné-Postel, Knee Society function and knee **Important outcomes** • Graft survival at 5 and 10 years • OCA failure at latest follow-up (median follow-up 6.3 years (range 1.9 to 16.8 years))
Thomas et al 2013 Retrospective case series Army Medical Center, Georgia, USA	61 patients (61 knees) with a medium to large osteochondral lesion No subgroups reported	**Intervention** Fresh OCA 33 concomitant procedures in 24 patients (21 osteotomy, 3 microfracture, 9 meniscal or ligamentous procedures) **Comparison** None	**Critical Outcomes** None reported **Important outcomes** Reported at latest follow-up (mean follow-up 46.2 +/- 13.4 months) • Surgical failure requiring revision **Safety**

			• Complications (timepoint not stated)

Abbreviations: ADL: Activities of Daily Living; IKDC: International Knee Documentation Committee score; KOOS: Knee Injury and Osteoarthritis Outcome Scores; mHSS: the modified Hospital for Special Surgery score; OCA: Osteochondral allograft; OCD: Osteochondritis Dissecans; QOL: Quality of Life; SF12: Short form 12 Health Survey; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

5. Results

In people with large osteochondral defects >2cm^2, what is the clinical effectiveness and safety of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Knee specific score **Certainty of evidence:** Very low	Knee specific scores are important to patients because they measure pain, symptoms, function in daily living, function in sport and quality of life, all of which can have a significant impact on patients. In total, seven case series (one prospective and six retrospective) reported non-comparative evidence for a range of knee specific outcome scores with mean follow-up ranging from 67 months to 15.5 years for people treated with OCA for large osteochondral defects. The scores used varied between studies and included the Knee Injury and Osteoarthritis Outcome Scores (KOOS), the International Knee Documentation Committee (IKDC) scores, the Knee Society – function (KS-F) and Knee Society – knee (KS-K) scores, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the modified Hospital for Special Surgery score (mHSS), and the modified Merle d'Aubigné-Postel (MAPS) score. The scores measure pain and various aspects of function and activities (see end of table for more details[a]). At up to two years and mean 7.29 +/- 3.30 years follow-up: • Two case series (Brown et al 2011, Cotter et al 2018) (n range = 24 to 38 knees) reported the **KOOS pain, symptoms and sport** scores. • Brown et al 2011 reported mean +/- SD scores at baseline, 6 months, 1 year and 2 years, with a p value comparing baseline vs 2 years. The scores at these time points for pain were 59 +/-17; 79 +/-17; 77 +/-18; 74 +/-22; p=0.028; for symptoms were 58 +/-16; 69 +/-20; 69 +/-21; 70 +/-20; p=0.172; and for sports were 37 +/-26; 65 +/-27; 59 +/-23; 57 +/-30; p=0.005. The scores for pain and sports showed statistically significant improvements between baseline and 2 years. The improvement in the symptoms score was not statistically significant. The score improvements for pain at 6 months and 1 year, and for sport at 6 months exceeded the minimum clinically important difference (MCID) defined in the PICO, but declined thereafter[7]. **(VERY LOW)** • Cotter et al 2018 found mean improvements in score between pre-op and latest follow-up of 20.8 (pain), 14.8 (symptoms) and 25.96 (sport) (all statistically significant improvements, p<0.001) at mean 7.29 +/- 3.30 years follow-up. The score improvements for pain and sport exceeded the MCID defined in the PICO. Cotter et al 2018 reported that the improvement in symptoms score exceeded the MCID but did not provide the MCID definition. **(VERY LOW)** At mean from 6 months to 11.0 (range 2.9 to 29) years follow-up: • Six case series (Brown et al 2011, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Sadr et al 2016) (n range= 23 to 137 knees) reported IKDC scores. • Four case series (Brown et al 2011, Cotter et al 2018, Gracitelli et al 2017, Sadr et al 2016) reported **IKDC total** score and all reported

[7] MCIDs defined in the PICO were: 16.7 for KOOS pain and 25 for KOOS sports/recreation before and after OCA

	statistically significant improvements. Brown et al 2011 reported mean +/- SD scores at baseline of 45 +/-11, 6 months of 57 +/-14, 1 year of 59 +/- 15 and 2 years of 62 +/-20; p<0.001 (comparing baseline vs 2 years). Cotter et al 2018 found a mean improvement at follow-up of 25.54 (p<0.0001); Gracitelli et al 2017 found a mean pre-op score of 32.9 and mean follow-up score of 54.3 (p=0.012) and Sadr et al 2016 found a mean (+/- SD) pre-op score of 44.2 +/- 17.5 and follow-up score of 82.3 +/- 15.8 (p<0.001). Cotter et al 2018 reported that the improvement exceeded the MCID but did not provide the MCID definition. **(VERY LOW)** • Four case series (Early et al 2018; Gortz et al 2010; Gracitelli et al 2017; Sadr et al 2016) reported **IKDC pain** score and all but one reported statistically significant improvements. Early et al 2018 found a mean pre-op score of 7.2 and mean follow-up score of 2.8 (p<0.001); Gortz et al 2010 found a mean pre-op score of 7.1 and mean follow-up score of 2.0 (p<0.001); Gracitelli et al 2017 found a mean pre-op score of 6.4 and mean follow-up score of 4.5 (p=0.055) and Sadr et al 2016 found a mean (+/- SD) pre-op score of 5.3 +/- 2.5 and follow-up score of 2.1 +/- 2.2 (p< 0.001). **(VERY LOW)** • Four case series (Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Sadr et al 2016) reported **IKDC function** score and all reported statistically significant improvements. Early et al 2018 found a mean pre-op score of 3.3 and mean follow-up score of 6.5 (p=0.005); Gortz et al 2010 found a mean pre-op score of 3.5 and mean follow-up score of 8.3 (p=0.002); Gracitelli et al 2017 found a mean pre-op score of 2.8 and mean follow-up score of 6.0 (p=0.001) and Sadr et al 2016 found a mean (+/- SD) pre-op score of 3.5 +/- 1.8 and follow-up score of 8.1 +/- 2.0 (p<0.001). **(VERY LOW)** At mean from 67 months to 11.0 (range 2.9 to 29) years follow-up: • Three case series (Early et al 2018, Gortz et al 2010, Sadr et al 2016) (n range=23 to 137 knees) reported the **Knee Society-function** score and all reported statistically significant improvements. Early et al 2018 found a mean pre-op score of 61.7 and mean follow-up score of 87.5 (p=0.0030); Gortz et al 2010 found a mean pre-op score of 60.0 and mean follow-up score of 85.7 (p=0.005), and Sadr et al 2016 found a mean (+/- SD) pre-op score of 72.3 +/- 18.6 and follow-up score of 95.7 +/- 9.6 (p<0.001). **(VERY LOW)** • One case series (Sadr et al 2016) (n=137 knees) reported the **Knee Society-knee** score with a mean (+/- SD) pre-op score of 81.1 +/- 14.8 and mean follow-up score of 94.3 +/- 8.8 (p<0.001), a statistically significant improvement. **(VERY LOW)** At mean 7.29 +/- 3.30 years follow-up: • One case series (Cotter et al 2018) (n=38 knees) reported a statistically significant improvement in the **WOMAC pain** score and **WOMAC stiffness** score (both p<0.0001); actual scores or change in scores were not reported. Cotter et al 2018 reported that the improvement in both scores did not exceed the MCID but did not provide the MCID definition. **(VERY LOW)** At mean from 67 (range 25 to 235) months to 6.3 (range 1.9 to 16.8) years follow-up: • Two case series (Gortz et al 2010; Sadr et al 2016) (n range = 25 to 137 knees) reported the **MAPS** scores and both reported statistically significant improvements. Gortz et al 2010 found a mean pre-op score of 11.3 and mean follow-up score of 15.8 (p<0.001) and Sadr et al 2016 found a mean (+/- SD) pre-op score of 13.6 +/- 2.0 and mean follow-up score of 16.8 +/- 1.5 (p< 0.001). **(VERY LOW)** At mean 15.5 (range 4.3 to 31.7) years follow-up:

	• One case series (Abolghasemian et al 2019) (n=60 knees) reported the **mHSS** score and found a statistically significant improvement. They found a mean pre-op score of 69 (range 48 to 85) and mean follow-up score of 85.5 (range 56 to 100), p < 0.001. **(VERY LOW)** **These studies provided very low certainty evidence that there is a statistically significant improvement in knee specific scores in patients undergoing OCA at between 2 years and mean 15.5 years follow-up after surgery. They do not provide any evidence about changes in knee specific scores for patients undergoing OCA compared to ACI with bone graft, ACI alone or no surgical treatment. Two studies provided very low certainty evidence that the improvement in two scores (KOOS pain and KOOS sport) exceeded the predefined MCID.**
Quality of life score **Certainty of evidence:** Very low	Quality of life score is important to patients because osteochondral defects may be associated with a significant reduction in quality of life. This measure helps inform patient-centred shared decision making and health policy. Disease specific quality of life questionnaires can provide information regarding improvement in symptoms. In total, two case series (one prospective and one retrospective) reported non-comparative results for quality of life in people treated with OCA for large osteochondral defects. Quality of life was measured using the SF12 and the KOOS QOL score[b]. At up to two years and mean 7.29 +/- 3.30 years follow-up: • Two case series (Brown et al 2011, Cotter et al 2018) (n range= 24 to 38 knees) reported the **KOOS knee-related QOL** score. Brown et al 2011 reported a mean +/- SD score at baseline of 23 +/-17, at 6 months of 47 +/-21, at 1 year of 49 +/-24, and at 2 years of 48 +/-22 (statistical test only reported between baseline vs 2 years; p<0.001, a statistically significant improvement). Cotter et al 2018 reported a statistically significant improvement in mean score of 20.88 (p<0.0001) at mean 7.29 years follow-up but actual scores were not reported. Cotter et al 2018 reported that the improvement in QOL score exceeded the MCID but did not provide the MCID definition. **(VERY LOW)** At mean 7.29 +/- 3.30 years follow-up: • One case series (Cotter et al 2018) (n=38 knees) reported the SF12-mental and SF12-physical scores. They found a statistically significant improvement in the **SF12-physical** score (p=0.002; actual scores and change in scores not reported) but no statistically significant change in the **SF12-mental** score (p=0.910). **(VERY LOW)** **These studies provided very low certainty evidence that there is a statistically significant improvement in the KOOS QOL score in patients with large osteochondral defects undergoing OCA at 2 years and at 7.29 years after surgery. They also provided very low certainty evidence that there is a statistically significant improvement in SF12-physical score, but no significant change in SF12-mental score in patients undergoing OCA for OCD at a mean of 7.29 years after surgery. They did not provide any evidence about quality of life for patients undergoing OCA compared to ACI with bone graft, ACI alone or no surgical treatment.**
Activities of daily living score **Certainty of evidence:** Very low	Activities of daily living (ADL) score is important to patients because it grades mobility, work and sports activities and therefore impacts on their daily function and ability. Activities of daily living refer to the basic skills needed to properly care for oneself and meet one's physical needs. In total, two case series (one prospective and one retrospective) reported non-comparative results for ADL in people treated with OCA for large osteochondral defects. ADL subscores, each consisting of 17 items, were reported from two knee specific scores[c]. At up to two years and mean 7.29 +/- 3.30 years follow-up:

	• Two case series (Brown et al 2011, Cotter et al 2018) (n range= 24 to 38 knees) reported the **KOOS (ADL)** score. Brown et al 2011 reported a mean +/- SD score at baseline of 69 +/-21, at 6 months, of 85 +/-16, at 1 year of 84 +/-16, and at 2 years of 83 +/-23 (statistical test only reported between baseline vs 2 years; not statistically significant, p=0.058). Cotter et al 2018 reported a statistically significant improvement in score of 20.88 (p<0.0001) at mean 7.29 years follow-up but actual scores were not reported. Cotter et al 2018 reported that the improvement in ADL score exceeded the MCID but did not provide the MCID definition. **(VERY LOW)** At mean 7.29 +/- 3.30 years follow-up: • One case series (Cotter et al 2018) (n=38 knees) reported the **WOMAC (function)** score. They reported a statistically significant improvement in score (p<0.0001) but actual scores and changes in scores were not reported. **(VERY LOW)** **These studies provided very low certainty evidence that there is not a statistically significant improvement in ADL scores in patients with large osteochondral defects undergoing OCA at 2 years, but there is a statistically significant improvement in ADL scores in patients undergoing OCA at a mean of 7.29 years after surgery. They do not provide any evidence about ADL for patients undergoing OCA compared to ACI with bone graft, ACI alone or no surgical treatment.**
Important outcomes	
Allograft survival rate at 5, 10, 15 and 20 years **Certainty of evidence:** Very low	Allograft survival rate is important to patients because longevity of the treatment will affect patient satisfaction as well as reduce the need for further intervention which may have negative outcomes and increased risks. In total, six retrospective case series reported non-comparative results for allograft survival rate in people treated with OCA for large osteochondral defects at various intervals between five and 20 years after surgery. Allograft survival rate at five years: • Six case series (Abolghasemian et al 2019, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Sadr et al 2016) (n range=28 to 149 knees) reported **allograft survival rate at 5 years**. They found survival rates of 90% (95%CI 83% to 94%), 97%, 90%, 89%, 82.6% and 95% respectively (CI reported where available). **(VERY LOW)** Allograft survival rate at 10 years: • Five case series (Abolghasemian et al 2019, Early et al 2018, Gracitelli et al 2017, Raz et al 2014, Sadr et al 2016) (n range=33 to 149 knees) reported **allograft survival rate at 10 years.** They found survival rates of 79% (95%CI 70% to 86%), 82%, 69.6%, 91% (95%CI 80% to 96%), and 93% respectively (CI reported where available). **(VERY LOW)** Allograft survival rate at 15 years: • Two case series (Abolghasemian et al 2019, Raz et al 2014) (n range=58 to 113 knees) reported **allograft survival rate at 15 years**. They found survival rates of 64% (95%CI 53% to 73%) and 84% (95%CI 50% to 81%) respectively. (**VERY LOW)** Allograft survival rate at 20 years: • Two case series (Abolghasemian et al 2019, Raz et al 2014) (n range=58 to 113 knees) reported **allograft survival rate at 20 years**. They found survival rates of 47% (95%CI 34% to 59%) and 69% (95%CI 50% to 81%) respectively. **(VERY LOW)** **These studies provided very low certainty evidence that allograft survival rate is around 82% to 97% at 5 years, around 70% to 93% at 10**

	years, around 64% to 84% at 15 years and around 47% to 69% at 20 years after OCA surgery in patients with large osteochondral defects.
Failure of transplantation **Certainty of evidence:** Very low	Failure of transplantation is important to patients because it can result in further treatment being required which will impact on patient satisfaction as well as recovery time. In total, eight retrospective case series reported non-comparative results for failure rates at between 46.2 months and 21.8 years after surgery for people treated with OCA for large osteochondral defects. While the details of definitions of failure varied across studies, most included revision or removal of the OCA, and/or conversion to TKA. The two studies reporting higher failure rates at shorter follow-up (Gracitelli et al 2017 and Gortz et al 2010) appeared to have used broader definitions of failure encompassing other types of surgery also. At mean 46.2 +/- 13.4 months follow-up: • One case series (Thomas et al 2013) (n=61 knees) reported a failure rate of 9.8%. **(VERY LOW)** At mean 67 (range 25 to 235) months follow-up: • One case series (Gortz et al 2010) (n=28 knees) reported a failure rate of 18%. **(VERY LOW)** At median 6.3 (range 1.9 to 16.8) years follow-up: • One case series (Sadr et al 2016) (n=149 knees) reported a failure rate of 8%. **(VERY LOW)** At median 6.6 (range 2 to 23.6) years follow-up: • One case series (Gracitelli et al 2017) (n=39 knees) reported a failure rate of 26%. **(VERY LOW)** At mean 7.29 +/- 3.30 years follow-up: • One case series (Cotter et al 2018) (n=39 knees) reported a failure rate of 5.1%. **(VERY LOW)** At mean 11 (range 2.9 to 29) years follow-up: • One case series (Early et al 2018) (n=33 knees) reported a failure rate of 27%. **(VERY LOW)** At mean 13.8 (range 1.7 to 34) years follow-up: • One case series (Abolghasemian et al 2019) (n=113 knees) reported a failure rate of 42%. **(VERY LOW)** At mean 21.8 (range 15 to 42) years follow-up: • One case series (Raz et al 2014) (n=58 knees) reported a failure rate of 22.4%. **(VERY LOW)** **These studies provided very low certainty evidence that failure rates ranged between 5.1% and 42% at time periods between 46.2 months and 21.8 years after OCA surgery in patients with large osteochondral defects. Definitions of failure rates varied and variations in failure rates across studies did not always appear to correspond with duration of follow-up.**
Safety	
Adverse reactions **Certainty of evidence:** Very low	Adverse reactions are important to patients because they will impact on their treatment choices and recovery and could have long term sequelae. In total, three retrospective case series reported non-comparative results for rates of various complications after surgery in people treated with OCA for large osteochondral defects. The time points at which complications were reported were not stated.

	• Three case series (Abolghasemian et al 2019, Cotter et al 2018, Thomas et al 2013) reported total complication rates of 2.7%, 10.3% and 8.2% respectively. The commonest complication was infection with rates of infection of 1.8%, 2.6% and 3.3% respectively. **(VERY LOW)** **These studies provided very low certainty evidence that complications occurred in between 2.7% to 10.3% of patients undergoing OCA for large osteochondral defects, and that the commonest complication was infection occurring in between 1.8% and 3.3% of patients. They do not provide any evidence about safety for patients undergoing OCA compared to ACI with bone graft, ACI alone or no surgical treatment.**

a. Summary of knee scores

Higher score is better for all scores apart from the IKDC pain subscore, for which higher score is worse.

- IKDC (International Knee Documentation Committee): The full IKDC includes 10 questions measuring symptoms, including pain (6 questions), sports activities (3 questions), ADL (1 question).
- KS (Knee Society Score): symptoms (3 items) (including pain (2 items)), functional activities (3 items - use of aids, standing, walking), standard activities (6 items), advanced activities (5 items), knee-related activities (3 items).
- KOOS (Knee injury and Osteoarthritis Outcome Score): symptoms (5 items), stiffness (2 items), pain (9 items), sports/ recreation (5 items), each rated on a 5-point scale.
- MAPS (modified Merle d'Aubigné-Postel): measures pain, gait and mobility, each on a 6-point scale. Minimum score 3, maximum score 18.
- mHSS (modified Hospital for Special Surgery) score reports: Pain intensity (5-point scale); Instability (3-point scale); Use of walking aids; Walking distance; Knee extension; Knee flexion; Effusion. Maximum score 100.
- WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index): pain (5 items), stiffness (2 items), each rated on a scale 0-4, max score 96.

b. QOL scores

Higher score is better for all scores

- SF12: 12 questions taken from the SF-36 Health Survey which are combined and weighted to report on mental and physical functioning subscales.
- KOOS QOL: 4 items on knee-related QOL: being aware of your knee, difficulty with your knee, lack of confidence in your knee, lifestyle modifications because of your knee.

c. ADL scores

Higher score is better for all scores

- KOOS ADL: 17 items which cover a range of ADL activities (eg. using stairs, sitting, standing, walking, getting dressed/ undressed, using bath/toilet, shopping, domestic tasks).
- WOMAC function: 17 items which cover a range of ADL activities (eg. using stairs, sitting, standing, walking, getting dressed/ undressed, using bath/toilet, shopping, domestic tasks).

Abbreviations: ACI: Autologous Chondrocyte Implantation; ADL: Activities of Daily Living; CI: Confidence interval; IKDC: International Knee Documentation Committee score; KS: Knee Society Score; KOOS: Knee injury and Osteoarthritis Outcome Score; MAPS: modified Merle d'Aubigné-Postel score; mHSS: modified Hospital for Special Surgery score; MCID: Minimum clinically important difference; OCA: Osteochondral allograft; OCD: Osteochondritis Dissecans; QOL: Quality of Life; SD: Standard deviation; TKA: Total knee arthroplasty; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

In people with large osteochondral defects >2cm^2, what is the cost effectiveness of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?

Outcome	Evidence statement
Cost Effectiveness	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of people that may benefit from fresh OCA more than the wider population of interest?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with OCA.

From the evidence selected,

a. What are the criteria used by the research studies to define osteochondral defects?
b. What size were the osteochondral defects?
c. Were patients who had osteoarthritis included in the studies?
d. Were patients who had previous cartilage repair included in the studies?

Question	Evidence statement
What are the criteria used by the research studies to define osteochondral defects?	The criteria used to define osteochondral defects were generally referred to within study inclusion criteria. Two studies (Early et al 2018, and Gortz et al 2010) of OCA in patients with steroid-associated osteonecrosis stated that they included patients with stage III-IV (modified Ficat/Arlet stage)[8] lesions secondary to steroid-associated necrosis of the femoral condyles. The authors described the lesions as 'advanced' but did not provide more details about how this classification was applied to patients with osteonecrosis of the knee. There were two studies of OCA in patients with OCD. Sadr et al 2016 referred to patients with 'type III or IV OCD' in their inclusion criteria, but with no further details of what this meant or how it was applied. Cotter et al 2018 referred to the ICD9 definition of OCD in their inclusion criteria, but with no further details. One study (Brown et al 2011) stated that they included patients with International Cartilage Repair Society (ICRS) grade 4 lesions[9]. Two studies (Abolghasemian et al 2019, and Raz et al 2014) used osteochondral lesion dimensions (both used >3 cm in diameter, >1 cm in depth) to define the lesions to be included in the study. Abolghasemian et al 2019 stated that lesions were posttraumatic, and Raz et al 2014 specified that they were posttraumatic or OCD, but there were no further details. Thomas et al 2013 referred only to 'medium to large osteochondral lesions' and Gracitelli et al 2017 to 'large osteochondral traumatic lesions due to fractures on the knee'. Neither provided further details on how these were defined or identified.
What size were the osteochondral defects?	Three studies defined lesion size by area. These were: • Mean lesion size 365mm^2 (Thomas et al 2013) • Average defect size 460.87 +/- 168.12 mm^2 (Cotter et al 2018) • Mean lesion size 5.7 cm^2 (range 1.5-15 cm^2) (Brown et al 2011).

[8] Ficat/ Arlet classification – originally a classification for osteonecrosis of the hip.
[9] ICRS Grade Characteristics: 0 Normal; 1 Nearly normal (soft indentation and/or superficial fissures and cracks); 2 Abnormal (lesions extending down to <50% of cartilage depth); 3 Severely abnormal (cartilage defects >50% of cartilage depth); 4 Severely abnormal (through the subchondral bone)

	Two studies defined the minimum dimensions of the lesion only, which in both were >3 cm in diameter, >1 cm in depth (Abolghasemian et al 2019, Raz et al 2014). Four studies defined graft area rather than lesion area. These were: • Mean allograft size 7.3 cm^2 (range 2.2-25 cm^2) (Sadr et al 2016) • Mean total allograft surface area 10.6 cm^2 (range 4.0–19.0 cm^2) (Early et al 2018) • Mean total allograft surface area 10.8 cm^2 (range 5.0–19.0 cm^2) (Gortz et al 2010) • Mean total allograft surface area 14.5 cm^2 (range 2–33 cm^2) (Gracitelli et al 2017).
Were patients who had osteoarthritis included in the research studies?	Eight of the studies did not state whether or not any of the included patients had osteoarthritis at the time of inclusion in the study. One study (Brown et al 2011) stated that 23 (64%) of the included subjects had focal osteoarthritic defects (idiopathic and posttraumatic types).
Were patients who had previous cartilage repair included in the studies?	Seven studies included patients who had had previous cartilage repair, including microfracture (Brown et al 2011, Cotter et al 2018, Early et al 2018, Gortz et al 2010, Gracitelli et al 2017, Sadr et al 2016, Thomas et al 2013). Two studies did not state whether or not patients had had previous cartilage repair (Abolghasemian et al 2019, and Raz et al 2014).
Abbreviations: ICD: International Classification of Disease; ICRS: International Cartilage Repair Society; OCA: Osteochondral allograft; OCD: Osteochondritis dissecans.	

6. Discussion

This review considered the evidence for the clinical effectiveness and safety of fresh OCA in patients with large osteochondral defects compared to autologous chondrocyte implantation (ACI) with bone graft, ACI alone or no surgical treatment. The critical outcomes of interest were knee specific scores, quality of life (QOL) scores and activities of daily living (ADL) scores. Important outcomes were allograft survival rate up to 20 years and failure of transplantation. Evidence was also sought on safety (adverse reactions) and cost effectiveness.

No comparative studies were identified. Evidence was available from nine case series including between 28 and 149 knees (between 22 and 135 patients). One was a prospective case series with 2-year follow-up and the remaining eight were retrospective with follow-up ranging from a mean of 46.2 months to 21.8 years after surgery. The studies used various definitions of osteochondral lesions, or none, and included patients with a range of underlying conditions causing the lesion including trauma, OCD and steroid-associated osteonecrosis. Studies were included where it was reported, or seemed very likely, that all or almost all lesions were osteochondral rather than chondral. Lesion size was reported in a variety of ways in five studies, not all of them defining a lower threshold for lesion area. Studies were included where it was reported, or seemed very likely, that all or almost all lesions exceeded 2cm^2 in area. Four studies reported graft area rather than lesion area, and these varied widely in size but all exceeded 2cm^2. All the studies were at high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

Seven of the studies were based in the USA, four of which came from the same unit and two of which reported outcomes for the same cohort at different time intervals. The two remaining studies came from the same unit in Canada.

Knee specific scores reported included the Knee injury and Osteoarthritis Outcome Score (KOOS), the International Knee Documentation Committee score (IKDC), the Knee Society score (KS), the modified Merle d'Aubigné-Postel score (MAPS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the modified Hospital for Special Surgery score (mHSS). They are all multi-item scales which assess various combinations of pain, symptoms, mobility and function, some divided into subscales which report these aspects separately and some combined as a single score. Two (the KOOS and WOMAC scales) include 17-item subscales measuring ADL and one (the KOOS scale) includes a 4-item subscale measuring knee-related QOL.

Seven studies reported knee specific scores and all provided very low certainty evidence. One study, the prospective case series by Brown et al 2011, reported knee specific scores at baseline and follow-up intervals up to 2 years. They followed up a cohort of 34 patients with Grade 4 International Cartilage Repair Society (ICRS) articular cartilage defects of the femoral condyle, reporting outcomes at six months, one year and two years. There was considerable loss to follow-up (10/34, 29%). They found statistically significant improvements in all but one knee scores measured at two years compared with baseline, but did not measure the statistical significance of changes at any of the other timepoints.

Knee specific scores measured at baseline and at latest follow-up were reported in six of the retrospective case series at between 67 months and 15.5 years follow-up. Almost all measures were reported to show a statistically significant improvement at the latest follow-up compared with baseline. Sample sizes for these measures ranged from 23 to 149 knees. While three of the studies appeared to have included all eligible patients with little or no loss

to follow-up, the other three excluded some eligible patients and/or had significant loss to follow-up. Most studies reported limited demographic and clinical information about the included subjects.

Only two studies reported the KOOS pain and KOOS sports scores for which minimum clinically important difference (MCID) levels were defined in the PICO; the MCIDs were 16.7 for KOOS pain and 25 for KOOS sports/recreation. In Brown et al 2011 the improvements in mean scores at six months and one year respectively were 20 and 18 for pain, and 28 and 22 for sports. The pain scores exceeded the MCID at six months and one year, and the sports score at six months, but both declined below the MCID threshold thereafter. In Cotter et al 2018 the reported improvements in mean scores at mean 7.29 years follow-up were 20.68 and 25.96 respectively, exceeding the MCID, although the actual scores were not reported.

Cotter et al 2018 also reported that improvements in IKDC and in KOOS symptoms, QOL and ADL scores achieved MCIDs, and that changes in WOMAC pain and symptoms subscores did not achieve MCIDs, but did not provide definitions of these MCID thresholds.

QOL scores were reported in two studies with very low certainty evidence. At mean 7.29 years follow-up Cotter et al 2018 reported a statistically significant improvement in the SF12-physical score, but no significant change in the SF12-mental score; actual scores were not reported. Brown et al 2011 and Cotter et al 2018 both reported statistically significant improvements in the KOOS QOL score at 2 years and mean 7.29 years follow-up respectively.

ADL scores were reported in two studies with very low certainty evidence, using the subscales of the KOOS and WOMAC knee specific scores. Brown et al 2011 found an improvement in KOOS ADL score which did not achieve statistical significance at two years after surgery, while Cotter et al 2018 found statistically significant improvements in both the KOOS ADL and WOMAC ADL scores at mean 7.29 years follow-up.

Apart from the MCID changes in KOOS scores, the clinical significance of the improvements in all other scores reported was not clear.

Six studies reported allograft survival at five years, five studies at 10 years, two studies at 15 years and two at 20 years. Overall graft survival decreased with each time interval from around 82%-97% at 5 years, to around 47%-69% at 20 years and around 59% at 25 years after surgery. Loss to follow-up varied across these studies but both studies reporting survival at more than 10 years had some loss to follow-up.

Graft failure in most studies was defined as revision or removal of the graft, and/or conversion to total knee arthroplasty, but two studies (Gortz et al 2010 and Gracitelli et al 2017) appeared to have more inclusive definitions including the need for other types of surgery. Failure rates reported in eight studies ranged between 5.1% and 42% at time periods between 46.2 months and 21.8 years after surgery. Variations in failure rates across studies did not always appear to correspond with duration of follow-up. The two studies with more comprehensive definitions of failure reported higher failure rates at shorter time intervals.

Complications relating to the surgery were reported in three studies (Abolghasemian et al 2019, Cotter et al 2018, Thomas et al 2013). Total complications rates ranged from 2.7% to 10.3%. The only type of complication reported across all three studies was infection, with rates from 1.8% to 3.3%.

In addition to the non-comparative nature of the case series study design a number of other factors which may have affected the outcomes have increased the uncertainty of the results. These include factors relating to the heterogeneity of study subjects and limited information provided about them:

- Studies used different definitions (or none) of osteochondral lesion and there was lack of clarity in most studies about how the lesions were diagnosed.
- Lesion size was defined in various ways; by dimensions (diameter and depth), by area, or by area of the graft used. The size of lesions varied widely across different studies.
- The underlying cause of the osteochondral lesion, where defined, varied across studies. There was no information about whether this is likely to affect the outcomes for individual patients.
- Mean age in individual studies ranged from 21 to 43 years; actual ages ranged from 11 to 72 years. Two studies included adults only and the remainder also included subjects aged under 17 years. No studies analysed different age groups separately.
- Most studies included very limited demographic or clinical information about the subjects.

In addition, factors relating to the conduct and reporting of the studies included:

- Incomplete inclusion of eligible subjects and/or considerable loss to follow-up was reported in some studies.
- Eight of the nine studies were retrospective analyses of prospectively collected patient data, adding additional potential biases due to risk of selection bias and incomplete reporting of the original cohort which may be harder to identify retrospectively.
- Most studies appeared to be carried out in a single centre and some included interventions carried out by a single surgeon. It is not clear how generalisable their findings might be to other settings.
- Eight studies reported that they included subjects who had had at least one previous procedure; in seven of the studies this included the majority of the study participants. One study did not comment on whether or not subjects had had previous procedures. The previous procedures included cartilage, meniscal and ligamentous procedures and osteotomies, but no studies reported outcomes separately for those who had had previous procedures.
- Eight studies reported that subjects had additional procedures at the same time as OCA. In two studies the procedures were bone grafts, and in the remaining six there were a range of procedures including osteotomy, meniscal allograft and ligament reconstruction. It is not possible to separate the effects of the OCA from the effects of these additional procedures. The ninth study did not state whether concomitant procedures were carried out.

7. Conclusion

This review included nine case series which provide very low certainty evidence on critical and important outcomes following fresh OCA for large osteochondral defects. All studies which reported knee specific scores found statistically significant improvements with varying durations of follow-up up to mean 15.5 years, but only two reported improvements which met the MCID threshold defined in the PICO, one at six months and a year (although this improvement was not maintained), and one at a mean of 7.29 years.

There was evidence of improvements in the KOOS QOL score in two studies and in QOL physical but not QOL mental scores in one study, and of improvements in ADL scores in two studies. Graft survival generally decreased over time across studies, but failure rates varied widely between studies and did not always appear to correspond with duration of follow-up. Complication rates were reported in three studies and were generally low, the commonest complication being infection.

All the evidence from these studies must be regarded as very low certainty due to their design, conduct and reporting. Study subjects were heterogeneous, with variations in age, definitions and size of osteochondral lesions (where defined) and underlying conditions. Many had concomitant interventions, the effects of which cannot be distinguished from the effects of OCA in the measurement of outcomes.

No comparative studies were identified so it is not possible to reach any conclusions about the outcomes of OCA in these patients compared with ACI with bone graft, ACI alone or no surgical treatment. There was also no evidence on cost effectiveness or on any subgroups who may benefit from OCA more than the general population of interest.

The studies identified for this review therefore provide very low certainty evidence that OCA in patients with large osteochondral defects may improve knee specific scores, but there is very little evidence on whether the improvements are clinically significant to patients. It is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of OCA compared with ACI with bone graft, ACI alone or no surgical treatment.

Appendix A PICO Document

The review questions for this evidence review are:

1. In people with large osteochondral defects >2cm^2, what is the clinical effectiveness of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?
2. In people with large osteochondral defects >2cm^2, what is the safety of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?
3. In people with large osteochondral defects >2cm^2, what is the cost effectiveness of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?
4. From the evidence selected, are there any subgroups of people that may benefit from fresh OCA more than the wider population of interest?
5. From the evidence selected,
    a. What are the criteria used by the research studies to define osteochondral defects?
    b. What size were the osteochondral defects?
    c. Were patients who had osteoarthritis included in the studies?
    d. Were patients who had previous cartilage repair included in the studies?

P –Population and Indication	People with large (>2cm^2) osteochondral defects of the knee joint in whom best supportive care has failed, irrespective of previous cartilage repair [Femoral, tibial and patellar defects within the knee are all relevant. Best supportive care would include non-surgical interventions such as pharmacological treatments, physiotherapy, weight management and lifestyle modification.] Subgroups - Adults vs. children - Those with previous failed cartilage repair - People with osteochondral defects who are not suitable for a bone graft (large uncontained defects) -People with previous meniscal transplants, unstable or maligned knee joints
I – Intervention	Fresh osteochondral allograft transplantation (OCA) [Fresh OCA is a surgical technique to treat large osteochondral defects (a focal area of damage that involves both the cartilage and a piece of underlying bone). The grafts are stored at 4 degrees or above (not frozen) and implanted within 28 days of harvest.]

C – Comparator(s)	1) Autologous chondrocyte implantation (ACI) with bone graft (sandwich technique) [In osteochondral defects a bone graft is required prior to the cartilage repair. ACI is a 2-stage process requiring extraction and growth of chondrocytes from biopsied healthy cartilage and then an operation to implant these cells.] 2) Autologous chondrocyte implantation (ACI) alone [When a bone graft is not possible ACI can be performed alone.] 3) No surgical treatment [For some patients no surgical treatment is possible until joint deterioration reaches the point of requiring total knee replacement.]
O – Outcomes	**<u>Clinical Effectiveness</u>** *Unless stated for the outcome, the minimum clinically important difference (MCID) is unknown* *<u>Critical to decision-making:</u>* • Knee specific score measured at 6, 12 and 24 months, including but not limited to the Knee injury and Osteoarthritis Outcome score (KOOS), Lysholm score and Cincinnati score *- The MCID is 16.7 for KOOS pain and 25 for KOOS sports/recreation before and after OCA (Ogura et al 2018)* *- This outcome is important to patients because it measures pain, symptoms, function in daily living, function in sport and quality of life, all of which can have a significant impact on patients.* • Quality of life score measured at 6, 12 and 24 months, including but not restricted to EQ-5D *- This outcome is important to patients because osteochondral defects may be associated with a significant reduction in quality of life. This measure helps inform the patient centred shared decision making and health policy. Disease specific quality of life questionnaires can provide information regarding improvement in symptoms.* • Activities of daily living score measured at 6, 12 and 24 months, including but not restricted to the Tegner activity scale *- This outcome is important to patients because it grades mobility, work and sports activities and therefore impacts on their daily function and ability. Activities of daily living refer to the basic skills needed to properly care for oneself and meet one's physical needs.*

	These are considered the outcomes most critical to decision making as they include the patient's perspective on the treatment's effect on their condition. *Important to decision-making:* • Allograft survival rate at 5, 10, 15 and 20 years *- This outcome is important to patients because longevity of the treatment will affect patient satisfaction as well as reduce the need for further intervention which may have negative outcomes and increased risks.* • Failure of transplantation which is defined as: - return of patient reported outcome measures score to within 10% of the pre-operative value - need for revision surgery (further cartilage repair or total knee replacement) *- This outcome is important to patients because it can result in further treatment being required which will impact on patient satisfaction as well as recovery time.* **Safety** • Adverse reactions (including but not restricted to infection, bleeding, deep vein thrombosis, reoperations) *- These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae.* **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2010-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2010 to 6 November 2020

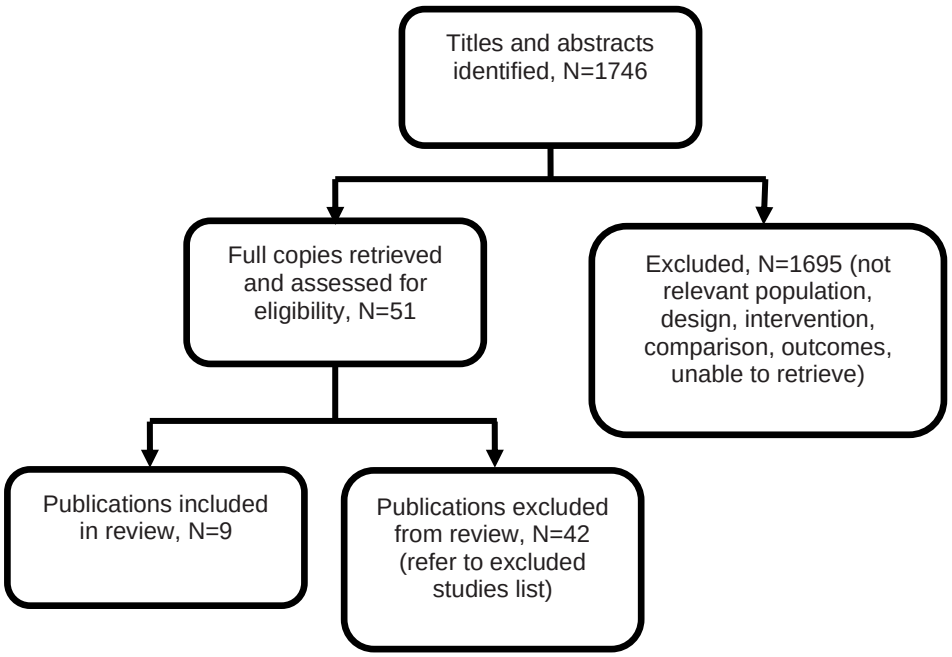
Medline search

# ▲	**Searches**
1	Knee injuries/
2	exp Knee Joint/
3	patella/
4	((chondral or osteochondral) adj2 (defect? or injur*)).ti,ab,kw.
5	(knee* or patella* or patello* or meniscus or meniscal).ti,ab,kw.
6	1 or 2 or 3 or 4 or 5
7	Allografts/
8	Transplantation, Homologous/ and Bone Transplantation/
9	((osteochondral or chondral) adj2 (allograft* or graft* or transplant*)).ti,ab,kw.
10	oca.ti,ab,kw.
11	7 or 8 or 9 or 10
12	6 and 11
13	exp animals/ not humans/
14	12 not 13
15	limit 14 to (english language and yr="2010 -Current")

Appendix C Evidence selection

The literature searches identified 1746 references. These were screened using their titles and abstracts and 51 references were obtained in full text and assessed for relevance. Of these, 9 references are included in the evidence summary. The remaining 42 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Familiari F, Cinque ME, Chahla J, et al. Clinical Outcomes and Failure Rates of Osteochondral Allograft Transplantation in the Knee: A Systematic Review. Am J Sports Med. 2018;46(14):3541-3549	Excluded. This systematic review included 19 studies, most of which included mixed populations of subjects with various aetiologies and it was not clear how many had osteochondral defects. Aggregate mean scores were reported for different combinations of studies, based on the scores used, not the included populations, but no significance measures were reported for the pooled outcomes. There was no separate analysis of outcomes for subjects with osteochondral defects only. Individual studies which were identified in the literature search were considered separately for inclusion in this review.
Mistry H, Metcalfe A, Smith N, et al. The cost-effectiveness of osteochondral allograft transplantation in the knee. Knee Surg Sports Traumatol Arthrosc. 2019;27(6):1739-1753	Excluded The survival model used in the analysis was based on the findings of Familiari et al (2018), therefore did not include only patients who had osteochondral defects.
Gracitelli GC, Meric G, Briggs DT, et al. Fresh osteochondral allografts in the knee: comparison of primary transplantation versus transplantation after failure of previous subchondral marrow stimulation. Am J Sports Med. 2015;43(4):885-891	Excluded This study included a mixed population and it was unclear how many subjects had osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Ackermann J, Merkely G, Shah N, Gomoll AH. Decreased Graft Thickness Is Associated With Subchondral Cyst Formation After Osteochondral Allograft Transplantation in the Knee. Am J Sports Med. 2019;47(9):2123-9.	Mixed population including both chondral and osteochondral defects. No separate analysis of outcomes for subjects with osteochondral lesions only.
Andrade R, Nunes J, Hinckel BB, Gruskay J, Vasta S, Bastos R, et al. Cartilage Restoration of Patellofemoral Lesions: A Systematic Review. Cartilage. 2019:1947603519893076.	Majority of patients across all studies (where reported) did not have osteochondral lesions. Only 7% of interventions were OCA.
Assenmacher AT, Pareek A, Reardon PJ, Macalena JA, Stuart MJ, Krych AJ. Long-term Outcomes After Osteochondral Allograft: A Systematic Review at Long-term Follow-up of 12.3 Years. Arthroscopy. 2016;32(10):2160-8.	Only 2/5 studies included patients with only osteochondral lesions. No pooled outcomes reported for patients with osteochondral lesions only.
Briggs DT, Sadr KN, Pulido PA, Bugbee WD. The Use of Osteochondral Allograft Transplantation for Primary Treatment of Cartilage Lesions in the Knee. Cartilage. 2015;6(4):203-7.	Mixed population including both chondral and osteochondral defects. No separate analysis of outcomes for subjects with osteochondral lesions only.
Chahal J, Gross AE, Gross C, Mall N, Dwyer T, Chahal A, et al. Outcomes of osteochondral allograft transplantation in the knee. Arthroscopy. 2013;29(3):575-88.	Studies included patients with various aetiologies and it was not clear how many had osteochondral lesions. No pooled outcomes reported for patients with osteochondral lesions only.
Chahla J, Sweet MC, Okoroha KR, Nwachukwu BU, Hinckel B, Farr J, et al. Osteochondral Allograft Transplantation in the Patellofemoral Joint: A Systematic Review. Am J Sports Med. 2019;47(12):3009-18.	Studies included some or all patients with chondral lesions. No pooled outcomes reported for patients with osteochondral lesions only.
Chalmers PN, Vigneswaran H, Harris JD, Cole BJ. Activity-Related Outcomes of Articular Cartilage Surgery: A Systematic Review. Cartilage. 2013;4(3):193-203.	Intervention was osteochondral autograft, not allograft.
Cotter EJ, Hannon CP, Christian DR, Wang KC, Lansdown DA, Waterman BR, et al. Clinical Outcomes of Multifocal Osteochondral Allograft Transplantation of the Knee: An Analysis of Overlapping Grafts and Multifocal Lesions. Am J Sports Med. 2018;46(12):2884-93.	Outcomes only reported for 2 different OCA methods with n=9 and n=15.
Crawford ZT, Schumaier AP, Glogovac G, Grawe BM. Return to Sport and Sports-Specific Outcomes After Osteochondral Allograft Transplantation in the Knee: A Systematic Review of Studies With at Least 2 Years' Mean Follow-Up. Arthroscopy. 2019;35(6):1880-9.	Studies included some or all patients with chondral lesions. Individual study outcomes only reported, no pooled outcomes.
De Caro F, Bisicchia S, Amendola A, Ding L. Large fresh osteochondral allografts of the knee: a systematic clinical and basic science review of the literature. Arthroscopy. 2015;31(4):757-65.	Types of lesions not described, unclear whether chondral or osteochondral. Individual study outcomes only reported, no pooled outcomes.
Enweze LC, Varshneya K, Sherman SL, Safran MR, Abrams GD. Risk of Subsequent Knee	Type of lesion unclear (database study). Various interventions including OCA.

Arthroplasty After Sports Medicine Procedures. J. 2020;4(8):e2000125.	
Familiari F, Cinque ME, Chahla J, et al. Clinical Outcomes and Failure Rates of Osteochondral Allograft Transplantation in the Knee: A Systematic Review. Am J Sports Med. 2018;46(14):3541-3549	Most studies included mixed populations of subjects with various aetiologies and it was not clear how many had osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.
Gracitelli GC, Meric G, Briggs DT, et al. Fresh osteochondral allografts in the knee: comparison of primary transplantation versus transplantation after failure of previous subchondral marrow stimulation. Am J Sports Med. 2015;43(4):885-891	The study included a mixed population and it was unclear how many had osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.
Gracitelli GC, Meric G, Pulido PA, McCauley JC, Bugbee WD. Osteochondral Allograft Transplantation for Knee Lesions after Failure of Cartilage Repair Surgery. Cartilage. 2015;6(2):98-105.	The study described a mixed population and it was unclear how many had osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.
Hinckel BB, Pratte EL, Baumann CA, Gowd AK, Farr J, Liu JN, et al. Patellofemoral Cartilage Restoration: A Systematic Review and Meta-analysis of Clinical Outcomes. Am J Sports Med. 2020;48(7):1756-72.	Subjects stated to have cartilage lesions, no details on whether any had osteochondral lesions. Only 6.6% of procedures were OCA.
Horton MT, Pulido PA, McCauley JC, Bugbee WD. Revision osteochondral allograft transplantations: do they work? Am J Sports Med. 2013;41(11):2507-11.	Subjects had revision OCA only which was not indicated as being in scope in the PICO.
Hurley ET, Davey MS, Jamal MS, Manjunath AK, Alaia MJ, Strauss EJ. Return-to-Play and Rehabilitation Protocols following Cartilage Restoration Procedures of the Knee: A Systematic Review. Cartilage. 2019:1947603519894733.	Subjects stated to have cartilage lesions, no details on whether any had osteochondral lesions. OCA outcomes reported in 7/179 studies.
Johnson CC, Johnson DJ, Garcia GH, Wang D, Pais M, Degen RM, et al. High Short-Term Failure Rate Associated With Decellularized Osteochondral Allograft for Treatment of Knee Cartilage Lesions. Arthroscopy. 2017;33(12):2219-27.	Focal cartilage lesions, including both chondral and osteochondral. No separate analysis of outcomes for subjects with osteochondral lesions only.
Jones KJ, Kelley BV, Arshi A, McAllister DR, Fabricant PD. Comparative Effectiveness of Cartilage Repair With Respect to the Minimal Clinically Important Difference. American Journal of Sports Medicine. 2019;47(13):3284-93.	Subjects had cartilage defects, no details on whether included osteochondral lesions.
Krych AJ, Pareek A, King AH, Johnson NR, Stuart MJ, Williams RJ, 3rd. Return to sport after the surgical management of articular cartilage lesions in the knee: a meta-analysis. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(10):3186-96.	Subjects had cartilage defects, no details on whether included osteochondral lesions. Only 3/44 studies included OCA.
Krych AJ, Robertson CM, Williams RJ, 3rd, Cartilage Study G. Return to athletic activity after osteochondral allograft transplantation in the knee. American Journal of Sports Medicine. 2012;40(5):1053-9.	Subjects had chondral or osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.

Lee S, Frank RM, Christian DR, Cole BJ. Analysis of Defect Size and Ratio to Condylar Size With Respect to Outcomes After Isolated Osteochondral Allograft Transplantation. Am J Sports Med. 2019;47(7):1601-12.	Subjects were described as having chondral and osteochondral lesions. It was unclear how many had osteochondral defects.
Levy YD, Görtz S, Pulido PA, McCauley JC, Bugbee WD. Do fresh osteochondral allografts successfully treat femoral condyle lesions? Clin Orthop Relat Res. 2013;471(1):231-7.	Subjects had both chondral and osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.
Lin KM, Wang D, Burge AJ, Warner T, Jones KJ, Williams RJ. Osteochondral Allograft Transplant of the Patella Using Femoral Condylar Allografts: Magnetic Resonance Imaging and Clinical Outcomes at Minimum 2-Year Follow-up. Orthop. 2020;8(10).	Cartilage lesions, not osteochondral lesions.
Mei XY, Alshaygy IS, Safir OA, Gross AE, Kuzyk PR. Fresh Osteochondral Allograft Transplantation for Treatment of Large Cartilage Defects of the Femoral Head: A Minimum Two-Year Follow-Up Study of Twenty-Two Patients. J Arthroplasty. 2018;33(7):2050-6.	Femoral head lesions only.
Melugin HP, Bernard CD, Camp CL, Saris DBF, Krych AJ. Bipolar Cartilage Lesions of the Knee: A Systematic Review of Techniques, Outcomes, and Complications. Cartilage. 2019:1947603519855761.	Subjects had cartilage lesions, not stated whether chondral or osteochondral but only a minority appear to be osteochondral. Individual study outcomes only reported, no pooled outcomes.
Meric G, Gracitelli GC, Görtz S, De Young AJ, Bugbee WD. Fresh osteochondral allograft transplantation for bipolar reciprocal osteochondral lesions of the knee. Am J Sports Med. 2015;43(3):709-14.	Subjects were stated to have bipolar chondral lesions, unclear how many had osteochondral lesions.
Merkely G, Ackermann J, Farina EM, VanArsdale C, Lattermann C, Gomoll AH. Shorter Storage Time Is Strongly Associated With Improved Graft Survivorship at 5 Years After Osteochondral Allograft Transplantation. American Journal of Sports Medicine. 2020;48(13):3170-6.	Subjects had chondral or osteochondral defects, no further details. No separate analysis of outcomes for subjects with osteochondral lesions only.
Mistry H, Metcalfe A, Smith N, et al. The cost-effectiveness of osteochondral allograft transplantation in the knee. Knee Surg Sports Traumatol Arthrosc. 2019;27(6):1739-1753	The survival model used in the analysis was based on the findings of Familiari et al (2018), therefore did not include only patients who had osteochondral defects.
Murphy RT, Pennock AT, Bugbee WD. Osteochondral allograft transplantation of the knee in the pediatric and adolescent population. Am J Sports Med. 2014;42(3):635-40.	About 20% of patients were described as having a chondral lesion or chondral injury. No separate analysis of outcomes for subjects with osteochondral lesions only.
Nimkingratana P, Brittberg M. Returning to Work After Articular Cartilage Repair Intervention: A Systematic Review. Orthop. 2020;8(3):2325967120905526.	Subjects had articular cartilage injury, not stated whether chondral or osteochondral lesions. 2/5 studies included OCA. Individual study outcomes only reported, no pooled outcomes.
Noyes FR, Barber-Westin SD. Advanced patellofemoral cartilage lesions in patients younger than 50 years of age: is there an ideal operative option? Arthroscopy. 2013;29(8):1423-36.	Subjects had articular cartilage injury, not stated whether chondral or osteochondral lesions. 2/18 studies included OCA.

Riff AJ, Huddleston HP, Cole BJ, Yanke AB. Autologous Chondrocyte Implantation and Osteochondral Allograft Transplantation Render Comparable Outcomes in the Setting of Failed Marrow Stimulation. American Journal of Sports Medicine. 2020;48(4):861-70.	Subjects stated to have chondral defects. No details were provided on whether any had osteochondral defects.
Robinson PG, Williamson T, Murray IR, Al-Hourani K, White TO. Sporting participation following the operative management of chondral defects of the knee at mid-term follow up: a systematic review and meta-analysis. J. 2020;7(1):76.	Subjects were athletes with chondral lesions, not stated whether any had osteochondral lesions. Only 4/29 studies included OCA.
Sadr KN, Pulido P, McCauley JC, Bugbee W. Fresh osteochondral allograft transplantation for osteochondritis dissecans of the knee. Orthop. 2014;2(3 Supplement 1).	Conference abstract.
Sochacki KR, Varshneya K, Calcei JG, Safran MR, Abrams GD, Donahue J, et al. Comparison of Autologous Chondrocyte Implantation and Osteochondral Allograft Transplantation of the Knee in a Large Insurance Database: Reoperation Rate, Complications, and Cost Analysis. Cartilage. 2020:1947603520967065.	Subjects in insurance database undergoing OCA or ACI, knee condition, type of lesion and indication for the procedure were not reported.
Tírico LEP, McCauley JC, Pulido PA, Bugbee WD. Lesion Size Does Not Predict Outcomes in Fresh Osteochondral Allograft Transplantation. Am J Sports Med. 2018;46(4):900-7.	Subjects had chondral or osteochondral lesions, no further details. No separate analysis of outcomes for subjects with osteochondral lesions only.
Tírico LEP, McCauley JC, Pulido PA, Bugbee WD. Osteochondral Allograft Transplantation of the Femoral Condyle Utilizing a Thin Plug Graft Technique. Am J Sports Med. 2019;47(7):1613-20.	Subjects had chondral or osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.
Tírico LEP, McCauley JC, Pulido PA, Demange MK, Bugbee WD. Is Patient Satisfaction Associated With Clinical Outcomes After Osteochondral Allograft Transplantation in the Knee? Am J Sports Med. 2019;47(1):82-7.	Subjects had chondral or osteochondral lesions. No separate analysis of outcomes for subjects with osteochondral lesions only.
Valtanen RS, Arshi A, Kelley BV, Fabricant PD, Jones KJ. Articular Cartilage Repair of the Pediatric and Adolescent Knee with Regard to Minimal Clinically Important Difference: A Systematic Review. Cartilage. 2020;11(1):9-18.	Only 1/12 studies reported OCA.
Wang D, Rebolledo BJ, Dare DM, Pais MD, Cohn MR, Jones KJ, et al. Osteochondral Allograft Transplantation of the Knee in Patients with an Elevated Body Mass Index. Cartilage. 2019;10(2):214-21.	Subjects stated to have Outerbridge grade III or IV lesions, which did not involve substantial bone loss.
Wang T, Wang DX, Burge AJ, Pais M, Kushwaha B, Rodeo SA, et al. Clinical and MRI Outcomes of Fresh Osteochondral Allograft Transplantation After Failed Cartilage Repair Surgery in the Knee. J Bone Joint Surg Am. 2018;100(22):1949-59.	Type of lesions not stated.

Appendix E Evidence Table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Abolghasemian M, Leon S, Lee PTH, Safir O, Backstein D, Gross AE, et al. Long-Term Results of Treating Large Posttraumatic Tibial Plateau Lesions with Fresh Osteochondral Allograft Transplantation. Journal of Bone & Joint Surgery - American Volume. 2019;101(12):1102-8. **Study location** Toronto, Canada **Study type** Retrospective case series **Study aim** To assess the long-term outcomes of fresh OCA transplantation for large posttraumatic tibial osteochondral defects in young, high-demand patients. **Study dates** 1972-2007	**Study inclusion criteria** Posttraumatic tibial plateau defect >3 cm diameter and >1 cm depth. Treated with fresh OCA, with or without realignment osteotomy. >2-year f/u, or <2-year f/u if OCA failed within 2 years. **Study exclusion criteria** Non-traumatic lesions. Lesions affecting both tibial plateau and the corresponding femoral condyle. **Total sample size** n=113 patients **Baseline characteristics** Mean age 43 years (range 24 to 72 years). 63/113 (56%) female. Mean of 1.46 (range 0 to 6) previous surgeries on affected knee; 109/113 had had previous open reduction and internal fixation.	**Intervention details** Fresh OCA (15 medial, 98 lateral tibial condyle). Mean or range of defect size not reported. 77 (68%) also had meniscal allograft, 74 (65%) also had realignment osteotomy. **Comparator details** No comparator.	**Critical outcomes** ***Knee specific score*** *mHSS[10] score* n=60 patients with surviving grafts. Duration of f/u for these 60 not stated; mean f/u for all 65 with surviving grafts reported to be 15.5 years (range 4.3 to 31.7 years) Mean pre-op score: 69 (range 48 to 85) Mean score at latest f/u: 85.5 (range 56 to 100) p < 0.001 Scores were completed in clinic for n=43, by phone for n=14, and by mail for n=3. **Important outcomes** ***Graft survival (Kaplan-Meier analysis)*** 5 Years (n not stated): 90% (95% CI 83% to 94%) 10 years (n=69): 79% (95% CI 70% to 86%) 15 years (n not stated): 64% (95% CI 53% to 73%)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Unclear 4. Unclear 5. No 6. No 7. No 8. Yes 9. No 10. Yes **Other comments:** As a case series this study does not include a comparator group and limited demographic and clinical information is included about the study subjects. 20 subjects who originally met the inclusion criteria were excluded because they were lost to f/u. Five subjects with surviving grafts were not included in the outcome measure; it was not stated whether these differed from the 60 included. The study reports outcomes from a single unit and it is not clear how

[10] mHSS (modified Hospital for Special Surgery) score reports: Pain intensity (5-point scale); Instability (3-point scale); Use of walking aids; Walking distance; Knee extension; Knee flexion; Effusion. Maximum score 100 (higher score better).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			20 years (n=18): 47% (95% CI 34% to 59%) ***OCA failure*** (conversion to TKA or repeat OCA) mean f/u 13.8 years (range 1.7 to 34 years) 48/113 (42%) (CI not reported) (n=46 converted to TKA, n=2 had repeat OCA) **Safety** ***Complications*** Timepoint not stated Infection: 2/113 (1.8%) (CI not reported) Non-union of allograft: 1/113 (0.9%) (CI not reported)	generalisable these might be to other settings. The clinical significance of the mean mHSS scores reported, and the change in scores, is not clear. There was no blinding of outcomes score measurement. Scores were completed by phone or mail rather than in person for 17/60 subjects; it is not stated whether all approaches have equal validity. **Source of funding:** Investigation performed at the Gluskin Granovsky Division of Orthopaedics, Mount Sinai Hospital, University of Toronto. The authors indicated that no external funding was received for any aspect of this work.
Brown D, Shirzad K, Lavigne SA, Crawford DC. Osseous Integration after Fresh Osteochondral Allograft Transplantation to the Distal Femur: A Prospective Evaluation Using Computed Tomography. Cartilage. 2011; 2(4):337-45. **Study location** Oregon, USA **Study type** Prospective case series	**Study inclusion criteria** Received OCA for grade 4 International Cartilage Repair Society (ICRS) articular cartilage defects of the femoral condyle. **Study exclusion criteria** Patients requiring compressive fixation for graft stability at the time of surgery. **Total sample size** n=34 patients	**Intervention details** Fresh OCA. Mean lesion size 5.7 cm^2 (range 1.5 to 15 cm^2). Nine (26%) had concurrent procedures (osteotomy, meniscus transplant or ligament reconstruction). **Comparator details**	**Critical outcomes** 2-year f/u. Mean +/- SD score at baseline; 6 months; 1 year; 2 years; p value (significance test only reported for baseline vs 2 years). Baseline n=34; 6-month n=32; 1-year n=26; 2-year n=24. ***Knee specific scores*** *KOOS[11] pain score* 59 +/-17; 79 +/-17 *; 77 +/-18*; 74 +/-22; p=0.028 *KOOS symptoms score*	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Unclear 4. Yes 5. No 6. No 7. Unclear 8. Yes 9. No 10. No

[11] KOOS (Knee injury and Osteoarthritis Outcome Score): symptoms (5 items), stiffness (2 items), pain (9 items), ADL function (17 items), sports/ recreation (5 items), knee-related QOL (4 items), each rated on a 5-point scale (higher score better) .

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study aim To prospectively assesses osseous integration and early clinical results following fresh OCA with single or multiple cylindrical grafts to the femoral condyle **Study dates** 2006-2008	**Baseline characteristics** Mean age 34.5 years (range 15 to 61 years). 25 (74%) male. Mean BMI 26.9 kg/m^2 (range 19.7 to 39.1 kg/m^2). Mean of 0.7 previous surgeries (n=25 previous surgeries, including 1 previous OCA). 23 (64%) of the included subjects had focal osteoarthritic defects (idiopathic and posttraumatic types).	No comparator.	58 +/-16; 69 +/-20; 69 +/-21; 70 +/-20; p=0.172 *KOOS sports score* 37 +/-26; 65 +/-27 *; 59 +/-23; 57 +/-30; p=0.005 *IKDC[12] score* 45 +/-11; 57 +/-14; 59 +/-15; 62 +/-20; p<0.001 * Exceeded the MCID defined in the PICO for this review The authors compared knee scores in those lost to f/u with the whole cohort. They reported that: Those lost to f/u between 6 months and 1 year (n=32 at 6 months, n=26 at 1 year) had statistically higher IKDC scores than those who remained in the study (67 v 53; p=0.012). Those lost to f/u between 1 and 2 years (n=26 at 1 year, n=24 at 2 years) had statistically lower KOOS pain (80 v 61; p=0.05), KOOS symptoms (53 v 75; p=0.012), KOOS QoL (54 v 23; p=0.017), and IKDC (63 v 42; p=0.014) scores than those who remained in the study. ***ADL score*** *KOOS ADL score[13]*	**Other comments:** As a case series this study does not include a comparator group and limited demographic and clinical information is included about the study subjects. The data were collected prospectively and outcomes are clearly reported at specific timepoints. There was no blinding of outcomes score measurement. Six subjects who originally met the inclusion criteria were excluded because of missing pre-op or f/u data. 10/34 (29%) were lost to f/u by 2 years. The authors compared knee scores in those lost to f/u with the whole cohort and reported those where there were statistically significant differences. They found that the significant differences were not consistent between the groups or over time, suggesting that no clear difference was found between those lost to f/u and those retained in the study. It appeared that the scores compared were those from the last f/u before loss to f/u, but this was not stated. Other scores, where there appear to have been no significant

[12] IKDC: The full International Knee Documentation Committee (IKDC) score includes 10 questions measuring symptoms, including pain (6 questions), sports activities (3 questions), ADL (1 question) (higher score better apart from the pain subscore when reported separately, for which higher score is worse).
[13] The KOOS ADL subscore has been reported separately as an ADL score as it includes 17 items which cover a range of ADL activities (eg. using stairs, sitting, standing, walking, getting dressed/ undressed, using bath/toilet, shopping, domestic tasks).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			69 +/-21; 85 +/-16; 84 +/-16; 83 +/-23; p=0.058 **QOL score** *KOOS knee-related QOL score*[14] 23 +/-17; 47 +/-21; 49 +/-24; 48 +/-22; p<0.001	differences between those lost and not lost to f/u, were not reported. The study reports outcomes from a single unit and it is not clear how generalisable these might be to other settings. The improvements in KOOS pain scores at 6 months and 1 year, and in KOOS sports score at 6 months, exceeded the MCID defined in the PICO for this review, but both declined below the MCID threshold thereafter. The clinical significance of the other mean scores reported, and the change in scores, is not clear. The largest improvement in all scores occurs between baseline and 6 months. However statistical tests were only reported for the difference between scores at baseline and at 2 years. **Source of funding:** This research project was completed at Oregon Health & Science University, Portland, Oregon, and supported by AlloSource Inc., Centennial, Colorado

[14] The KOOS QOL subscore has been reported separately as a QOL score as it includes 4 items on knee-related QOL: being aware of your knee, difficulty with your knee, lack of confidence in your knee, lifestyle modifications because of your knee.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Cotter EJ, Frank RM, Wang KC, Totlis T, Poland S, Meyer MA, et al. Clinical Outcomes of Osteochondral Allograft Transplantation for Secondary Treatment of Osteochondritis Dissecans of the Knee in Skeletally Mature Patients. Arthroscopy. 2018;34(4):1105-12. **Study location** Chicago, USA **Study type** Retrospective case series **Study aim** To report clinical outcomes of OCA for skeletally mature patients with OCD lesions of the knee in whom prior surgical intervention has failed **Study dates** 2002-2014	**Study inclusion criteria** Skeletally mature. Undergoing OCA for OCD. Procedures by a single surgeon. **Study exclusion criteria** Underwent concomitant bone graft. Use of DeNovo NT graft. **Total sample size** n=37 patients (39 knees) **Baseline characteristics** Mean age 26.01 +/- 9.96 years (range 15.78 to 49.25 years). 26 (70%) male. Number of knees with failed articular cartilage procedures: 32 (82.1%). <u>Mean +/- SD</u> Number of previous surgeries: 2.3 +/- 1.3 procedures (all had at least one). BMI: 26.54 +/- 4.77 kg/m^2 Duration of symptoms: 4.54 +/- 4.38 years.	**Intervention details** Fresh OCA. Average defect size 460.87 +/- 168.12 mm^2. 11/37 had concomitant procedures (meniscal allograft or osteotomy). **Comparator details** No comparator.	**Critical outcomes** Mean f/u 7.29 +/- 3.30 years ***Knee specific scores*** (n=38 knees (36 patients)) Mean improvement, pre-op to f/u; p value. Actual scores not reported. *IKDC* * 25.54, p<0.0001 *KOOS subscores* * *Pain* ** 20.68, p<0.0001 *Symptoms* 14.28, p<0.0001 *Sport* ** 25.96, p<0.0001 *The authors reported that these all achieved published levels for MCID but did not provide the MCID definitions. ** Exceeded the MCID defined in the PICO for this review *WOMAC[15] pain***, overall score:* Score improved but actual scores not reported, p value of mean improvement in score <0.0001 *WOMAC stiffness*** score:* Score improved but actual scores not reported, p value of mean improvement in score =0.002	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. No 6. No 7. Unclear 8. No 9. No 10. No **Other comments:** As a case series this study does not include a comparator group and limited demographic and clinical information is included about the study subjects. Four eligible subjects were excluded because they were lost to f/u. It reports outcomes from procedures by a single surgeon and it is not clear how generalisable these might be to other surgeons and settings. There was no blinding of outcomes score measurement. Outcomes are incompletely reported, and pre-op and f/u outcome scores are not reported. Change in score is reported for some outcomes, and significance of the change in score (p value) for some

[15] Western Ontario and McMaster Universities Osteoarthritis Index: pain (5 items), stiffness (2 items), ADL function (17 items), each rated on a scale 0-4, max score 96 (higher score better).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			The authors reported that these did not achieve MCID, but did not provide the MCID definitions. ***QOL (n=38 knees (36 patients)) *SF12[16] physical*: Score improved but actual scores not reported, p value of mean improvement in score =0.002 *SF12 mental*: Score did not change significantly but actual scores not reported, p value of mean change in score =0.910 *KOOS Knee-related QOL** Mean improvement, pre-op to f/u; 30.56, p<0.0001 ***ADL*** (n=38 knees (36 patients)) *KOOS ADL**: Mean improvement 20.88, p<0.0001 *WOMAC function[17]:* score not reported, p value of mean improvement in score <0.0001 **Important outcomes** ***Graft Survival*** (n = 38 knees) 5 years: 97% (CI not reported) ***Failure*** (revision OCA, gross appearance of graft failure on second-look	outcomes, but these are not consistently reported for all outcomes. The clinical significance of the changes in scores is not clear although the authors reported that the changes in IKDC and KOOS scores achieved MCID. The change in KOOS pain and sports scores exceed the MCID defined in the PICO for this review. **Source of funding:** No comment on source of funding.

[16] SF12: 12 questions taken from the SF-36 Health Survey which are combined and weighted to report on mental and physical functioning subscales
[17] The WOMAC function score has been reported separately as an ADL score as it includes 17 items which cover a range of ADL activities (eg. using stairs, sitting, standing, walking, getting dressed/ undressed, using bath/toilet, shopping, domestic tasks).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			arthroscopy, or conversion to arthroplasty) 2/39 knees (5.1%) (CI not reported) **Safety** ***Complications*** 4/37 patients (11%) (CI not reported) (one infection, one wound dehiscence, one acute haematoma, one transient peroneal nerve palsy)	
Early S, Tirico LEP, Pulido PA, McCauley JC, Bugbee WD. Long-Term Retrospective Follow-up of Fresh Osteochondral Allograft Transplantation for Steroid-Associated Osteonecrosis of the Femoral Condyles. Cartilage. 2018: 1947603518809399. **Study location** California, USA **Study type** Retrospective case series **Study aim** To evaluate the extent to which fresh osteochondral allografts can (1) prevent or postpone need for prosthetic arthroplasty and (2) maintain long-term clinically meaningful decrease in pain and improvement in	**Study inclusion criteria** OCA for steroid-associated osteonecrosis of the femoral condyles. Age <50 years at time of OCA. Minimum 2 years post-surgery. **Study exclusion criteria** None stated. **Total sample size** n=25 patients (33 knees) **Baseline characteristics** Average age 25 years (range 16 to 48 years). 22 (66.7%) knees female. Mean BMI 21.8 kg/m^2 (range 17.1 to 28.1 kg/m^2). All had history of a medical diagnosis requiring prednisone use exceeding doses of 20 mg per day. Fifteen of 33 (45.5%) knees had an average of 1.5 previous surgeries, (range 1 to 5).	**Intervention details** Fresh OCA. Mean total allograft surface area 10.6 cm^2 (range 4.0 to 19.0 cm^2). 19/33 (58%) also had bone graft. **Comparator details** No comparator.	**Critical outcomes** Mean f/u 11.0 years (range 2.9 to 29 years) ***Knee specific scores*** n=23 knees Mean pre-op score; mean f/u score; p value. *IKDC pain* 7.2; 2.8; p<0.001 *IKDC function* 3.3; 6.5; p=0.005 *Knee Society function* [18] 61.7; 87.5; p=0.003 **Important outcomes** ***Graft Survival* (n=33 knees)** 5 years: 90% (CI not reported) 10 years: 82% (CI not reported) ***Failure* (n=33 knees)**	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. Yes 8. Yes 9. No 10. No **Other comments:** As a case series this study does not include a comparator group and limited demographic information is included about the study subjects. The authors reported that all eligible patients were included except one who had died since the procedure. It reports outcomes from a single unit and it is not clear how

[18] Knee Society Score: symptoms (3 items) (including pain (2 items)), functional activities (3 items - use of aids, standing, walking), standard activities (6 items), advanced activities (5 items), knee-related activities (3 items).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
function at mean 11-year follow-up **Study dates** 1984-2013			(defined as requiring revision OCA transplantation or conversion to arthroplasty) 9/33 (27%) (CI not reported)	generalisable these might be to other settings. Significance measures were lacking for some outcomes. The clinical significance of the mean scores reported, and the change in scores, is not clear. There was no blinding of outcomes score measurement. Scores were completed by mail rather than in person for an unspecified number of subjects; it is not stated whether this has equal validity. **Source of funding:** No comment on source of funding.
Gortz S, De Young AJ, Bugbee WD. Fresh osteochondral allografting for steroid-associated osteonecrosis of the femoral condyles. Clin Orthop. 2010;468(5):1269-78. **Study location** California, USA **Study type** Retrospective case series **Study aim** To investigate whether fresh osteochondral allografts would (1) heal to host bone in the presence of osteonecrosis, (2) provide a clinically meaningful decrease in pain and	**Study inclusion criteria** OCA for osteoarticular lesions secondary to steroid-associated osteonecrosis of the femoral condyles. Age <50 years at time of OCA. Minimum 2 years post-surgery. **Study exclusion criteria** None stated. **Total sample size** n=22 patients (28 knees) **Baseline characteristics** Average age 24.3 years (range 16 to 44 years). 16 (73%) female. Mean BMI 21 kg/m^2 (range 17.1 to 28.1 kg/m^2).	**Intervention details** Fresh OCA. Mean total allograft surface area 10.8 cm^2 (range 5.0 to 19.0 cm^2). 18/28 (64%) also had bone graft. **Comparator details** No comparator.	**Critical outcomes** Minimum f/u 25 months (mean 67 months; range 25 to 235 months) ***Knee specific scores*** Mean pre-op score; mean f/u score; p value. *IKDC pain (*n=22 knees) 7.1; 2.0; p<0.001 *IKDC function (*n=22 knees) 3.5; 8.3; p=0.002 *Modified Merle d'Aubigné-Postel* (n=25 knees) 11.3; 15.8; p<0.001 *Knee Society function (*n=unclear) 60.0; 85.7; p=0.005	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. Yes 8. Yes 9. No 10. No **Other comments:** As a case series this study does not include a comparator group and limited demographic information is included about

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
improvement in function, and (3) prevent or postpone the need for prosthetic arthroplasty **Study dates** 1984-2006	History of a medical diagnosis requiring prednisone use exceeding doses of 20 mg per day. Fourteen (50%) knees had an average of 1.5 previous surgeries (range 1 to 5).		**Important outcomes** Mean f/u 67 months; range 25 to 235 months ***Graft Survival*** 25/28 (89%) (CI not reported) ***Failure*** (defined as requiring additional surgery) 5/28 (18%) (CI not reported)	the study subjects. The authors reported that all eligible patients were included except one who had died since the procedure. It reports outcomes from a single unit and it is not clear how generalisable these might be to other settings. There was no blinding of outcomes score measurement. Significance measures were lacking for some outcomes. The clinical significance of the mean scores reported, and the change in scores, is not clear. Scores were completed in person for 16 patients (19 knees) and by telephone for six patients; it is not stated whether all approaches have equal validity. **Source of funding:** No comment on source of funding.
Gracitelli GC, Tirico LE, McCauley JC, Pulido PA, Bugbee WD. Fresh Osteochondral Allograft Transplantation for Fractures of the Knee. Cartilage. 2017; 8(2):155-61. **Study location** California, USA **Study type** Retrospective case series	**Study inclusion criteria** OCA for osteochondral lesions after knee fracture. Minimum 2 years f/u. **Study exclusion criteria** None stated. **Total sample size** n=39 patients (39 knees) **Baseline characteristics** 24 (62%) male.	**Intervention details** Fresh OCA. Mean total allograft surface area 14.5 cm^2 (range 2 to 33 cm^2). 12/39 (43.6%) had a concomitant meniscal allograft. There were 23 other concomitant procedures (number of	**Critical outcomes** Median f/u 6.6 years (range 2 to 23.6 years) ***Knee specific scores*** (n=29 knees with graft in situ at latest f/u) Mean (+/- SD) pre-op score; mean (+/- SD) f/u score; p value. *IKDC pain* 6.4 ± 2.3; 4.5 ± 3.1; p=0.055	This study was appraised using the JBI checklist for case series. 1. Yes 2. Unclear 3. Unclear 4. Yes 5. No 6. No 7. No 8. Yes 9. No 10. No

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study aim To evaluate functional outcomes and survivorship of OCA transplantation among patients with knee fractures who were eligible for OCA transplantation as a salvage treatment option **Study dates** 1986-2011	Average age 34 years (range 16 to 54 years). Mean BMI 28.4 kg/m^2 (range 19.6 to 42.1 kg/m^2). 36/39 (92.3%) knees had an average of 2.6 previous surgeries (range 1 to 9).	knees/patients not stated). **Comparator details** No comparator.	*IKDC function* 2.8 +/- 2.0; 6.0 +/- 2.6; p=0.001 *IKDC total* 32.9 +/- 16.6; 54.3 +/- 26.0; p=0.012 *Modified Merle d'Aubigné-Postel* [19] 11.3 +/- 1.6; 14.6 +/- 2.8; p<0.001 *Knee Society function* 56.1 +/- 23.9; 73.1 +/- 21.5; p=0.003 **Important outcomes** ***Graft Survival*** (n=39 knees) 5 years: 82.6% (CI not reported) 10 years: 69.6% (CI not reported) ***Failure*** (n=39 knees) (defined as requiring additional surgery and considered OCA failure) 10/39 (26%) (CI not reported)	**Other comments:** As a case series this study does not include a comparator group and limited demographic and clinical information is included about the study subjects. All eligible subjects appear to have been included. There was no description of how the osteochondral lesions were identified. It reports outcomes from a single unit and it is not clear how generalisable these might be to other settings. There was no blinding of outcomes score measurement. Significance measures were lacking for some outcomes. The clinical significance of the mean scores reported, and the change in scores, is not clear. **Source of funding:** No comment on source of funding.
Raz G, Safir OA, Backstein DJ, Lee PT, Gross AE. Distal Femoral Fresh Osteochondral Allografts: Follow-up at a Mean of Twenty-two Years. Journal of Bone & Joint Surgery - American Volume. 2014; 96(13):1101-7.	**Study inclusion criteria** Had undergone a unipolar osteochondral transplant to the femoral condyle more than 15 years previously. Aged <50 years at time of surgery. Posttraumatic osteochondral or OCD defect limited to the distal	**Intervention details** Fresh OCA. Mean or range of defect size not reported.	**Important outcomes** Mean f/u 21.8 years (range 15 to 42 years) ***Graft survival*** (n=58) % survival, 95% CI: 10 Years: 91% (95% CI 80% to 96%) 15 years: 84% (95% CI 71% to 91%) 20 years: 69% (95% CI 50% to 81%)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Unclear 3. Unclear 4. Yes 5. No 6. No

[19] Modified Merle d'Aubigné-Postel: measures pain, gait and mobility, each on a 6-point scale. Minimum score 3, maximum score 18 (higher score better).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study location Toronto, Canada **Study type** Retrospective case series **Study aim** To examine the long-term survival and clinical outcomes of fresh osteochondral allograft for posttraumatic and osteochondritis dissecans defects in the knee **Study dates** 1972-1995	aspect of the femur (unipolar), > 3 cm in diameter, > 1 cm in depth. **Study exclusion criteria** Degenerative disease affecting more than one compartment or more than one articular surface. **Total sample size** n=58 patients (58 knees) **Baseline characteristics** Mean age 28 years (range 11 to 48 years). Cause of lesion: Traumatic: 44 (76%) OCD: 14 (24%) Not stated whether any had had previous surgery.	36 (62%) had concomitant osteotomy. **Comparator details** No comparator.	***Failure*** (n=58) (Graft removal, re-graft, or TKA) 13/58 (22.4%) (CI not reported)	7. No 8. Yes 9. No 10. Yes **Other comments:** As a case series this study does not include a comparator group and limited information is included about the clinical and demographic background of the study subjects. Five subjects from the original cohort of 63 were reported lost to f/u. There was no description of how the osteochondral lesions were identified. There was no blinding of outcomes score measurement. Patients lacking outcome data within the previous twelve months were contacted, and a f/u visit was arranged or a questionnaire was administered over the telephone or by mail. It is not stated how many patients this applied to and whether all approaches have equal validity. **Source of funding:** No comment on source of funding.
Sadr KN, Pulido PA, McCauley JC, Bugbee WD. Osteochondral Allograft Transplantation in Patients With Osteochondritis	**Study inclusion criteria** Patients who underwent OCA transplantation for OCD at	**Intervention details** Fresh OCA.	**Critical outcomes** Median f/u 6.3 years (range 1.9 to 16.8 years)	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Dissecans of the Knee. Am J Sports Med. 2016;44(11):2870-5. **Study location** California, USA **Study type** Retrospective case series **Study aim** To determine the clinical outcome for patients who received fresh OCA transplantation for the surgical management of OCD after the failure of other treatments **Study dates** 1997-2013	Scripps Health. Minimum 2-year f/u. **Study exclusion criteria** F/u < 2years **Total sample size** n=135 patients (149 knees) **Baseline characteristics** Median age 21 years (range 12 to 55 years). 75.8% male. 81% had at least 1 previous surgery (range 1 to 7).	Mean allograft size 7.3 cm^2 (range 2.2 to 25 cm^2). It was not reported whether or not any subjects had concomitant procedures. **Comparator details** No comparator.	***Knee specific score*** (n=137 knees with graft in situ at latest f/u) Mean (+/- SD) pre-op score; mean (+/- SD) f/u score; p value. *Modified Merle d'Aubigné-Postel* 13.6 +/- 2.0; 16.8 +/- 1.5 p< 0.001 *IKDC pain* 5.3 +/- 2.5; 2.1 +/- 2.2 p< 0.001 *IKDC function* 3.5 +/- 1.8; 8.1 +/- 2.0 p<0.001 *IKDC total* 44.2 +/- 17.5; 82.3 +/- 15.8 p<0.001 *Knee Society Score – Function* 72.3 +/- 18.6; 95.7 +/- 9.6 p<0.001 *Knee Society Score – Knee* 81.1 +/- 14.8; 94.3 +/- 8.8 p<0.001 **Important outcomes** ***Graft survival*** (n= 149 knees) 5 years: 95% (CI not reported) 10 years: 93% (CI not reported) ***OCA failure*** (revision or removal of the graft) 12/149 knees (8%) (CI not reported)	3. Unclear 4. Unclear 5. Yes 6. No 7. No 8. Yes 9. No 10. No **Other comments:** As a case series this study does not include a comparator group and limited clinical and demographic information is included about the study subjects. All eligible subjects appear to have been included. There was no description of how the osteochondral lesions were identified. There was no blinding of outcomes score measurement. It reports outcomes from procedures in a single institution and it is not clear how generalisable these might be to other settings. Significance measures were lacking for some outcomes. The clinical significance of the mean scores reported, and the change in scores, is not clear. **Source of funding:** The study was partially funded by a non-commercial grant from Scripps Clinic Medical Group (an internal funding source).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Thomas D, Shaw KA, Waterman BR. Outcomes After Fresh Osteochondral Allograft Transplantation for Medium to Large Chondral Defects of the Knee. Orthop. 2019; 7(3):v 2325967119832299. **Study location** Army Medical Center, Georgia, USA **Study type** Retrospective case series **Study aim** To evaluate the efficacy and functional outcomes of OCA for medium to large osteochondral defects of the knee in physically active United States military service members **Study dates** 2009-2013	**Study inclusion criteria** Active-duty US Army servicemembers. OCA for a medium to large osteochondral lesion (>2 cm^2). Minimum 2-year f/u. **Study exclusion criteria** Non-military beneficiaries. Inadequate health record documentation. **Total sample size** n=61 patients (61 knees) **Baseline characteristics** 52 (85%) male. Mean age 31.7 +/- 8.0 years. 43 (70.5%) BMI <30 kg/m^2 20 (32.8%) smokers. Race: White 30 (49.2%) Black 16 (26.2%) Asian 2 (3.3%) Unknown 13 (21.3%) 39 (63.9%) had undergone at least 1 prior procedure (total of 58 prior therapeutic procedures).	**Intervention details** Fresh OCA. Mean lesion size 365mm^2 33 concomitant procedures were performed in 24 patients. No further details on types of procedures. **Comparator details** No comparator.	**Important outcomes** Mean f/u 46.2 +/- 13.4 months ***Failure*** *Surgical failure requiring revision* Defined as a revision chondral or osteochondral procedure and/or subsequent arthroplasty. 6 (9.8%) (CI not reported) **Safety** ***Complications*** (time point not reported) Infection: 2 (3.3%) (CI not reported) Arthrofibrosis: 2 (3.3%) (CI not reported) Fracture: 1 (1.6%) (CI not reported) Total: 5 (8.2%) (CI not reported)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Unclear 3. Unclear 4. Unclear 5. No 6. Yes 7. Unclear 8. Yes 9. No 10. No **Other comments:** As a case series this study does not include a comparator group and limited information is included about the clinical background of the study subjects. There was no description of the type or cause of the osteochondral lesions, or how they were identified. There was no blinding of outcomes score measurement. No significance measures were reported. A significant number of potentially eligible subjects (54) appear to have been excluded for unspecified reasons. It reports outcomes for active-duty US Army service members and it is not clear how generalisable these might be to other groups or settings. **Source of funding:**

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				No comment on source of funding.

Abbreviations: ADL: Activities of Daily Living; BMI: Body Mass Index; CI: Confidence interval; f/u: follow-up; ICRS: International Cartilage Repair Society; IKDC: International Knee Documentation Committee; JBI: Joanna Briggs Institute; KOOS: Knee injury and Osteoarthritis Outcome Score; KS: Knee Society score; MAPS: modified Merle d'Aubigné-Postel; MCID: Minimum clinically important difference; mHSS: modified Hospital for Special Surgery score; OCA: Osteochondral allograft; OCD: Osteochondritis dissecans; pre-op: pre-operative; QOL: Quality of life; SD: Standard deviation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Table 1: Question: In people with large osteochondral defects >2cm^2, what is the clinical effectiveness and safety of fresh OCA compared to ACI with bone graft, ACI alone or no surgical treatment?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	OCA	Comparator	Result		
Knee-specific score									
KOOS: pain at 6 months (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	32 knees (32 patients)	None	At baseline: 59 +/-17 At 6 months: 79 +/-17 (exceeds MCID threshold) No statistical test	Critical	Very low
KOOS: pain at 1 year f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	26 knees (26 patients)	None	At baseline: 59 +/-17 At 1 year: 77 +/-18 No statistical test	Critical	Very low
KOOS: pain at 2 years f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	24 knees (24 patients)	None	At baseline: 59 +/-17 At 2 years: 74 +/-22 p value (baseline vs 2 years): p=0.028	Critical	Very low
KOOS: pain at mean 7.29 +/- 3.30 years f/u (mean improvement in score)									
1 case series	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Mean improvement 20.68, p<0.0001 (exceeds MCID threshold)	Critical	Very low

Cotter et al 2018									
KOOS: symptoms at 6 months f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations [1]	Serious limitations[2]	Not applicable	Not calculable	32 knees (32 patients)	None	At baseline: 58 +/-16 At 6 months: 69 +/-20 No statistical test	Critical	Very low
KOOS: symptoms at 1 year f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations [1]	Serious limitations[2]	Not applicable	Not calculable	26 knees (26 patients)	None	At baseline: 58 +/-16 At 1 year: 69 +/-21 No statistical test	Critical	Very low
KOOS: symptoms at 2 years f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations [3]	Serious limitations[2]	Not applicable	Not calculable	24 knees (24 patients)	None	At baseline: 58 +/-16 At 2 years: 70 +/-20 p value (baseline vs 2 years): p=0.172	Critical	Very low
KOOS: symptoms at mean 7.29 +/- 3.30 years f/u (mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Mean improvement 14.28, p<0.0001	Critical	Very low
KOOS: sport at 6 months f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations [1]	Serious limitations[2]	Not applicable	Not calculable	32 knees (32 patients)	None	At baseline: 37 +/-26 At 6 months: 65 +/-27 No statistical test	Critical	Very low
KOOS: sport at 1 year f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series	Very serious	Serious limitations[2]	Not applicable	Not calculable	26 knees (26 patients)	None	At baseline: 37 +/-26 At 1 year: 59 +/-23 No statistical test	Critical	Very low

Brown et al 2011	limitations [1]								
KOOS: sport at 2 years f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	24 knees (24 patients)	None	At baseline: 37 +/-26 At 2 years: 57 +/-30 p value (baseline vs 2 years): p=0.005	Critical	Very low
KOOS: sport at mean 7.29 +/- 3.30 years f/u (mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Mean improvement 25.96, p<0.0001 (exceeds MCID threshold)	Critical	Very low
IKDC (total score) at 6 months f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations [1]	Serious limitations[2]	Not applicable	Not calculable	32 knees (32 patients)	None	At baseline: 45 +/-11 At 6 months: 57 +/-14 No statistical test	Critical	Very low
IKDC (total score) at 1 year f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations [1]	Serious limitations[2]	Not applicable	Not calculable	26 knees (26 patients)	None	At baseline: 45 +/-11 At 1 year: 59 +/-15 No statistical test	Critical	Very low
IKDC (total score) at 2 years f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	24 knees (24 patients)	None	At baseline: 45 +/-11 At 2 years: 62 +/-20 p value (baseline vs 2 years): p<0.001	Critical	Very low
IKDC (total score) at median 6.3 years f/u (range 1.9-16.8 years) (mean +/- SD pre-op and f/u scores) (benefit indicated by higher score)									
1 case series	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	137 knees (patients ns)	None	Pre-op score: 44.2+/-17.5 F/u score: 82.3+/-15.8 p<0.001	Critical	Very low

Sadr et al 2016									
IKDC (total score) at median 6.6 years f/u (range 2-23.6 years) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Gracitelli et al 2017	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	29 knees (29 patients)	None	Pre-op score: 32.9 F/u score: 54.3 p=0.012	Critical	Very low
IKDC (total score) at mean 7.29 +/- 3.30 years f/u (mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Mean improvement 25.54, p<0.0001	Critical	Very low
IKDC (pain) at mean 67 months f/u (range 25–235 months) (mean pre-op and f/u scores) (benefit indicated by lower score)									
1 case series Gortz et al 2010	Serious limitations[6]	Serious limitations[2]	Not applicable	Not calculable	n=22 knees	None	Pre-op score: 7.1 F/u score: 2.0 p<0.001	Critical	Very low
IKDC (pain) at median 6.3 years f/u (range 1.9-16.8 years) (mean +/- SD pre-op and f/u scores) (benefit indicated by lower score)									
1 case series Sadr et al 2016	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	137 knees (patients ns)	None	Pre-op score: 5.3+/ 2.5 F/u score: 2.1+/-2.2 p< 0.001	Critical	Very low
IKDC (pain) at median 6.6 years f/u (range 2-23.6 years) (mean pre-op and f/u scores) (benefit indicated by lower score)									
1 case series Gracitelli et al 2017	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	29 knees (29 patients)	None	Pre-op score: 6.4 F/u score: 4.5 p=0.055	Critical	Very low
IKDC (pain) at mean 11.0 years f/u (range 2.9-29 years) (mean pre-op and f/u scores) (benefit indicated by lower score)									
1 case series	Serious limitations[6]	Serious limitations[2]	Not applicable	Not calculable	23 knees (patients ns)	None	Pre-op score: 7.2 F/u score: 2.8 p<0.001	Critical	Very low

Early et al 2018									
IKDC (function) at mean 67 months f/u (range 25–235 months) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Gortz et al 2010	Serious limitations[6]	Serious limitations[2]	Not applicable	Not calculable	n=22 knees	None	Pre-op score: 3.5 F/u score: 8.3 p=0.002	Critical	Very low
IKDC (function) at median 6.3 years f/u (range 1.9-16.8 years) (mean +/- SD pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Sadr et al 2016	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	137 knees (patients ns)	None	Pre-op score: 3.5+/-1.8 F/u score: 8.1+/-2.0 p<0.001	Critical	Very low
IKDC (function) at median 6.6 years f/u (range 2-23.6 years) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Gracitelli et al 2017	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	29 knees (29 patients)	None	Pre-op score: 2.8 F/u score: 6.0 p=0.001	Critical	Very low
IKDC (function) mean 11.0 years f/u (range 2.9-29 years) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Early et al 2018	Serious limitations[6]	Serious limitations[2]	Not applicable	Not calculable	23 knees (patients ns)	None	Pre-op score: 3.3 F/u score: 6.5 p=0.005	Critical	Very low
Knee Society (function) at mean 67 months f/u (range 25–235 months) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Gortz et al 2010	Serious limitations[6]	Serious limitations[2]	Not applicable	Not calculable	Unclear (total n=28 knees (22 patients))	None	Pre-op score: 60.0 F/u score: 85.7 p=0.005	Critical	Very low
Knee Society (function) at median 6.3 years f/u (range 1.9-16.8 years) (mean (+/- SD) pre-op and f/u scores) (benefit indicated by higher score)									
1 case series	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	137 knees (patients ns)	None	Pre-op score: 72.3+/-18.6 F/u score: 95.7+/-9.6 p<0.001	Critical	Very low

Sadr et al 2016									
Knee Society (function) at mean 11.0 years f/u (range 2.9-29 years) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Early et al 2018	Serious limitations[6]	Serious limitations[2]	Not applicable	Not calculable	23 knees (patients ns)	None	Pre-op score: 61.7 F/u score: 87.5 p=0.003	Critical	Very low
Knee Society (knee) at median 6.3 years f/u (range 1.9-16.8 years) (mean (+/- SD) pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Sadr et al 2016	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	137 knees (patients ns)	None	Pre-op score: 81.1+/-14.8 F/u score: 94.3+/-8.8 p<0.001	Critical	Very low
WOMAC (pain) at mean 7.29 +/- 3.30 years f/u (p value of mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Score not reported (improved), p<0.0001	Critical	Very low
WOMAC (stiffness) at mean 7.29 +/- 3.30 years f/u (p value of mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Score not reported (improved), p=0.002	Critical	Very low
Modified Merle d'Aubigné-Postel at mean 67 months f/u (range 25–235 months) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Gortz et al 2010	Serious limitations[6]	Serious limitations[2]	Not applicable	Not calculable	25 knees (patients ns)	None	Pre-op score: 11.3 F/u score: 15.8 p<0.001	Critical	Very low
Modified Merle d'Aubigné-Postel at median 6.3 years f/u (range 1.9-16.8 years) (mean (+/- SD) pre-op and f/u scores) (benefit indicated by higher score)									
1 case series	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	149 knees (135 patients)	None	Pre-op score: 13.6+/-2.0 F/u score: 16.8+/-1.5 p<0.001	Critical	Very low

Sadr et al 2016									
mHSS at mean 15.5 years f/u (range 4.3 to 31.7 years) (mean pre-op and f/u scores) (benefit indicated by higher score)									
1 case series Abolghasemian et al 2019	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	60 knees (60 patients)	None	Pre-op score: 69 (range 48 to 85) F/u score: 85.5 (range 56 to 100). p<0.001	Critical	Very low
Quality of life score									
SF12 – mental at mean 7.29 +/- 3.30 years f/u (p value of mean change in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Score not reported (no significant change), p=0.910	Critical	Very low
SF12 – physical at mean 7.29 +/- 3.30 years f/u (p value of mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Score not reported (improved), p=0.002	Critical	Very low
KOOS knee-related QOL at 6 months f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	32 knees (32 patients)	None	At baseline: 23 +/-17 At 6 months: 47 +/-21 No statistical test	Critical	Very low
KOOS knee-related QOL at 1 year f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	26 knees (26 patients)	None	At baseline: 23 +/-17 At 1 year: 49 +/-24 No statistical test	Critical	Very low

KOOS knee-related QOL at 2 years f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	24 knees (24 patients)	None	At baseline: 23 +/-17 At 2 years: 48 +/-22 p value (baseline vs 2 years): p<0.001	Critical	Very low
KOOS knee-related QOL at mean 7.29 +/- 3.30 years f/u (mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Mean improvement 30.56, p<0.0001	Critical	Very low
Activities of daily living score									
KOOS: ADL at 6 months f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	32 knees (32 patients)	None	At baseline: 69 +/-21 At 6 months: 85 +/-16 No statistical test	Critical	Very low
KOOS: ADL at 1 year f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	26 knees (26 patients)	None	At baseline: 69 +/-21 At 1 year: 84 +/-16 No statistical test	Critical	Very low
KOOS: ADL at 2 years f/u (mean +/- SD) (benefit indicated by higher score)									
1 case series Brown et al 2011	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	24 knees (24 patients)	None	At baseline: 69 +/-21 At 2 years: 83 +/-23 p value (baseline vs 2 years): p=0.058	Critical	Very low
KOOS: ADL at mean 7.29 +/- 3.30 years f/u (mean improvement in score)									
1 case series	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Mean improvement 20.88, p<0.0001	Critical	Very low

Cotter et al 2018									
WOMAC: function at mean 7.29 +/- 3.30 years f/u (p value of mean improvement in score)									
1 case series Cotter et al 2018	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	38 knees (36 patients)	None	Score not reported (improved), p<0.0001	Critical	Very low
Allograft survival rate									
Allograft survival rate at 5 years									
1 case series Abolghasemian et al 2019	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	113 knees (113 patients)	None	90% (95% CI 83% to 94%)	Important	Very low
1 case series Cotter et al 2018	Very serious limitations [7]	Serious limitations[2]	Not applicable	Not calculable	39 knees (37 patients)	None	97% (CI not reported)	Important	Very low
1 case series Early et al 2018	Serious limitations[8]	Serious limitations[2]	Not applicable	Not calculable	33 knees (25 patients)	None	90% (CI not reported)	Important	Very low
1 case series Gortz et al 2010	Serious limitations[8]	Serious limitations[2]	Not applicable	Not calculable	28 knees (22 patients)	None	89% (CI not reported) (at mean 67 months)	Important	Very low
1 case series Gracitelli et al 2017	Very serious limitations[9]	Serious limitations[2]	Not applicable	Not calculable	39 knees (39 patients)	None	82.6% (CI not reported)	Important	Very low
1 case series	Very serious limitations[9]	Serious limitations[2]	Not applicable	Not calculable	149 knees (135 patients)	None	95% (CI not reported)	Important	Very low

Sadr et al 2016									
Allograft survival rate at 10 years									
1 case series Abolghasemian et al 2019	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	113 knees (113 patients)	None	79% (95% CI 70% to 86%)	Important	Very low
1 case series Early et al 2018	Serious limitations[8]	Serious limitations[2]	Not applicable	Not calculable	33 knees (25 patients)	None	82% (CI not reported)	Important	Very low
1 case series Gracitelli et al 2017	Very serious limitations[9]	Serious limitations[2]	Not applicable	Not calculable	39 knees (39 patients)	None	69.6% (CI not reported)	Important	Very low
1 case series Raz et al 2014	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	58 knees (58 patients)	None	91% (95% CI 80% to 96%)	Important	Very low
1 case series Sadr et al 2016	Very serious limitations[9]	Serious limitations[2]	Not applicable	Not calculable	149 knees (135 patients)	None	93% (CI not reported)	Important	Very low
Allograft survival rate at 15 years									
1 case series Abolghasemian et al 2019	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	113 knees (113 patients)	None	64% (95% CI 53% to 73%)	Important	Very low
1 case series	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	58 knees (58 patients)	None	84% (95% CI 71% to 91%)	Important	Very low

Raz et al 2014									
Allograft survival rate at 20 years									
1 case series Abolghasemian et al 2019	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	113 knees (113 patients)	None	47% (95% CI 34% to 59%)	Important	Very low
1 case series Raz et al 2014	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	58 knees (58 patients)	None	69% (95% CI 50% to 81%)	Important	Very low
Failure of transplantation									
Surgical failure requiring revision at mean follow-up 46.2 months									
1 case series Thomas et al 2019	Very serious limitations[10]	Serious limitations[2]	Not applicable	Not calculable	61 knees (61 patients)	None	9.8% (6/61) (CI not reported)	Important	Very low
Failure rate at mean follow-up 67 months									
1 case series Gortz et al 2010	Serious limitations[8]	Serious limitations[2]	Not applicable	Not calculable	28 knees (22 patients)	None	18% (5/28) (CI not reported)	Important	Very low
Failure rate at median follow-up 6.3 years									
1 case series Sadr et al 2016	Very serious limitations[9]	Serious limitations[2]	Not applicable	Not calculable	149 knees (135 patients)	None	8% (12/149) (CI not reported)	Important	Very low
Failure rate at mean follow-up 6.6 years									
1 case series	Very serious limitations[9]	Serious limitations[2]	Not applicable	Not calculable	39 knees (39 patients)	None	26% (10/39) (CI not reported)	Important	Very low

Gracitelli et al 2017									
Failure rate at mean follow-up 7.29 years									
1 case series Cotter et al 2018	Very serious limitations[7]	Serious limitations[2]	Not applicable	Not calculable	39 knees (37 patients)	None	5.1% (2/39) (CI not reported)	Important	Very low
Failure rate at mean follow-up 11 years									
1 case series Early et al 2018	Serious limitations[8]	Serious limitations[2]	Not applicable	Not calculable	33 knees (25 patients)	None	27% (9/33) (CI not reported)	Important	Very low
Failure rate at mean follow-up 13.8 years									
1 case series Abolghasemian et al 2019	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	113 knees (113 patients)	None	42% (48/113) (CI not reported)	Important	Very low
Failure rate at mean follow-up 21.8 years									
1 case series Raz et al 2014	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	58 knees (58 patients)	None	22.4% (13/58) (CI not reported)	Important	Very low
Safety									
Complications (time period not stated)									
1 case series Abolghasemian et al 2019	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	113 knees (113 patients)	None	Infection: 2/113 (1.8%) Non-union of allograft: 1/113 (0.9%) Total: 3/113 (2.7%)	Important	Very low

1 case series Cotter et al 2018	Very serious limitations[7]	Serious limitations[2]	Not applicable	Not calculable	39 knees (37 patients)	None	Infection: 1 (2.6%) Wound dehiscence: 1 (2.6%) Acute haematoma:1 (2.6%) Transient peroneal nerve palsy: 1 (2.6%) Total 4/39 (10.3%)	Important	Very low
1 case series Thomas et al 2019	Very serious limitations[10]	Serious limitations[2]	Not applicable	Not calculable	61 knees (61 patients)	None	Infection: 2 (3.3%) Arthrofibrosis: 2 (3.3%) Fracture: 1 (1.6%) Total: 5/61 (8.2%)	Important	Very low
Abbreviations: ADL: Activities of Daily Living; CI: Confidence interval; f/u: follow-up; IKDC: International Knee Documentation Committee score; KOOS: Knee injury and Osteoarthritis Outcome Score; KS: Knee Society score; MAPS: modified Merle d'Aubigné-Postel score; MCID: Minimum clinically important difference; mHSS: modified Hospital for Special Surgery score; ns: not stated; OCA: Osteochondral allograft; OCD: Osteochondritis dissecans; pre-op: pre-operative; QOL: Quality of life; SD: Standard deviation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index									

1 Bias: very serious limitations due to unclear reporting of study participants, lack of clarity on how condition identified, loss to f/u and lack of statistical test
2 Indirectness: serious indirectness due to lack of comparator group
3 Bias: very serious limitations due to unclear reporting of study participants, lack of clarity on how condition identified and loss to f/u
4 Bias: very serious limitations due to unclear reporting of study participants, loss to f/u and incomplete reporting of outcomes
5 Bias: very serious limitations due to unclear reporting of study participants and lack of clarity on how condition identified
6 Bias: serious limitations due to some lack of detail in reporting of study participants
7 Bias: very serious limitations due to unclear reporting of study participants, loss to f/u, incomplete reporting of outcomes and lack of statistical test
8 Bias: serious limitations due to some lack of detail in reporting of study participants and lack of statistical test
9 Bias: very serious limitations due to unclear reporting of study participants, lack of clarity on how condition identified and lack of statistical test
10 Bias: very serious limitations due to unclear reporting of study participants, incomplete inclusion of study participants, lack of clarity on how the condition was defined and identified and lack of statistical test

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4

	components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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