Interventional procedure overview of single-step scaffold insertion for repairing symptomatic chondral knee defects

Contents

Table 1 Abbreviations

Abbreviation	Definition
ACI	Autologous chondrocyte implantation
ADL	Activities of daily living
AMIC	Autologous matrix induced chondrogenesis
CI	Confidence interval
ICRS	International cartilage regeneration and joint preservation society
IKDC	International knee documentation committee
IQR	Interquartile range
KOOS	Knee injury and osteoarthritis outcome score
mACI	Matrix-induced autologous chondrocyte implantation
MCID	Minimal clinically important difference
MD	Mean difference
MOCART	Magnetic resonance observation of cartilage repair tissue
OA	Osteoarthritis
OAT	Osteochondral autograft transplantation
OR	Odds ratio
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SF-36	36 item short form survey
SMD	Standardised mean difference
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster universities arthritis index

Indications and current treatment

Chondral cartilage is the material that covers the end of the bones in the knee joint, to protect them from friction when moving. Damage to this cartilage (chondral knee defect) can cause symptoms such as knee pain and stiffness, and reduced mobility. Untreated full-thickness cartilage lesions may be associated with significant pain and, eventually, arthritis. This is a major cause of disability.

There are several approaches to managing chondral knee defects. Surgical options depend on the characteristics of the person and the defect. There are 2 main categories of procedure:

- Procedures that mainly aim for symptom relief include:
  - debridement
  - osteotomy
  - knee replacement.
- Procedures that aim for symptom relief and also to re-establish the cartilage surface include:
  - marrow stimulation techniques (such as Pridie drilling and microfracture)
  - mosaicplasty
  - OAT
  - focal articular resurfacing implants
  - ACI (in which chondrocytes harvested from the knee are cultured and implanted into the damaged cartilage).

Sometimes mACI is done. This is a 2-step procedure because cells have to be cultured outside the body. The cells are harvested for culturing in the first operation, then the cultured cells and scaffold are introduced in the second.

Unmet need

Damage to articular cartilage is common and unlikely to heal spontaneously because the cartilage does not have a blood supply. Surgical options like microfracture can be done in 1 procedure but are designed for small lesions. Options like ACI and mACI are designed for bigger lesions but need 2 procedures a few weeks apart because cells need to be extracted and cultured before being implanted. Scaffold insertion without cultured cell implantation has the potential advantage of being a single-step procedure and may be better for larger lesions than microfracture alone.

What the procedure involves

In this procedure, a scaffold is put into the area of damaged cartilage to encourage cells to grow into new cartilage. This is a single-step procedure because the cells are not cultured outside the body. A range of techniques can be used to introduce the cells that grow into new cartilage, supported by the scaffold. For example, tiny holes can be drilled into the bone (microfracture) to release the cells, or substances like bone marrow aspirate can be put into the area of damage. Whichever method is done, it is always done in the same operation as the scaffold insertion.

There are different types of scaffold and ways of doing the procedure. For example, some scaffolds are solid and some are injectable gels. Some of the solid scaffolds must be cut to size and applied over the defect. Other scaffolds are a standard size and shape, and are implanted into the subchondral bone in the damaged area. The procedure aims to repair the damaged cartilage, reduce symptoms and keep the joint working.

Outcome measures

The main outcomes included KOOS, IKDC, VAS, SF-36, Lysholm, Tegner, WOMAC and MOCART scores. The measures are detailed in the following paragraphs.

KOOS

A 42-item patient-reported outcome measure of knee and associated problems. It includes questions that assess short- (within a week) and long-term (up to decades) problems. It has 5 domains: 1) pain frequency and severity during functional activities; 2) symptoms such as the severity of knee stiffness and the presence of swelling, grinding or clicking, catching, and range of motion restriction; 3) difficulty experienced during ADL; 4) difficulty experienced with sport and recreational activities; and 5) knee-related quality of life. Each question is on a 5-point Likert scale and the final score is calculated on a scale from 0 (extreme knee problems) to 100 (no knee problems).

IKDC (subjective)

An 18-item patient-reported outcome measure of overall functioning with 3 subscales: knee symptoms, knee function and sports activities. Scores range from 0 (lowest level of function and worst symptoms) to 100 (highest level of function and no symptoms).

VAS (pain)

A patient-reported rating scale for pain, most commonly ranging from 0 (no pain) to 10 (worst pain). Some studies used a 0- to 100-point scale. This is referred to as VAS throughout the overview.

SF-36

A generic patient-reported quality of life measure. There are 36 items in 8 subscales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The overall score is from 0 to 100. Higher scores indicate better quality of life.

Lysholm score

An 8-question scale that assesses knee function in daily life but not in sports and recreational activity. Each question is scored on a scale from 0 to 10, with a total possible score of 100. Higher scores indicate better function.

Tegner score

A patient-reported assessment of (sporting) activity for people with knee injuries. Scores range from 0 (disability caused by the injury) to 10 (able to play competitive sport).

WOMAC

A patient-reported scale used for evaluating hip and knee OA. It is a 24-item scale with 3 subscales: pain (range 0 to 20), stiffness (range 0 to 8) and physical function (range 0 to 68). High scores indicate worse pain, stiffness and physical function.

IKDC Knee Examination Form (objective)

A form completed by a healthcare professional that covers 7 domains and is scored on 3 domains: effusion, passive motion deficit and ligament examination. Each domain is scored as normal, nearly normal, abnormal and severely abnormal. This is referred to as the IKDC (objective) throughout the overview.

MOCART

A standardised scoring system for evaluating cartilage repair from MRI findings. There are 11 domains of assessment and the overall score ranges from 0 to 100. Higher scores indicate better repair.

Evidence summary

Population and studies description

This interventional procedures overview is based on about 7,000 people from 5 systematic review and meta-analyses (Migliorini 2022a, Kim 2020a, Migliorini 2022b, Tan 2023, da Cunha 2020), a systematic review and network meta-analysis (Migliorini 2021a), 4 RCTs (Altschuler 2023, Kim 2020b, Kon 2018, de Girolamo 2019), a 5-year follow-up analysis of an RCT (Shive 2015) and a registry study with up to 7-year follow up (Gille 2021). There was significant overlap between the studies included in the meta-analyses. The RCT of 24 people (de Girolamo 2019) was included in 4 meta-analyses, the 5-year follow up of an RCT (Shive 2015) was included in 1 meta-analysis and the registry study (Gille 2021) was included in 2 meta-analyses. Among the RCTs listed, about 328 of 535 people had the procedure. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 12 studies as the key evidence in table 2 and table 3, and lists 69 other relevant studies in table 5.

The key evidence includes explicit comparisons between the procedure and several other procedures that can be used for this indication, or between different methods of doing the procedure. This is the reason for including several meta-analyses even if some or all studies overlap. The meta-analysis of 18 studies (Migliorini 2022a) and the meta-analysis of 29 studies (Kim 2020a) both compared the procedure with microfracture, but only 5 studies overlapped between these reviews. This may be because there were subtle differences in

the inclusion criteria for these reviews. The meta-analysis by Migliorini (2022b) compared the procedure with mACI. The network meta-analysis compared using a scaffold without cultured cell implantation after microfracture with microfracture alone, ACI, mACI and OAT (Migliorini 2021a) but only included 5 studies with this procedure because of the requirement for level 1 or 2 evidence. The meta-analysis by Tan (2023) compared outcomes between the procedure being done with open surgery or with an arthroscopic approach. The meta-analysis of 10 studies by da Cunha (2020) is not comparative but includes 3 studies that were not included in any of the other meta-analyses. This is the only meta-analysis that calls the procedure 'enhanced microfracture' and not 'autologous matrix-induced chondrogenesis', but all studies do use a scaffold. This is discussed in more detail in the procedure details section.

Other inclusion criteria relating to the characteristics of the defect varied between studies. Some studies excluded multiple lesions that were touching or in different locations, lesions over a certain size, or whether the person was having concomitant surgeries such as high tibial osteotomy or other surgical management. The meta-analysis comparing arthroscopic with open surgery for this procedure (Tan 2023), the RCTs of 251 people (Altschuler 2023) and 24 people (de Girolamo 2019), and the registry study (Gille 2021) only included grade 3 or higher lesions. Two RCTs only included people if they had a certain level of pain (Altschuler 2023 and Shive 2015). The meta-analysis by da Cunha (2020) primarily focused on tibiofemoral lesions but did include some other lesions in other locations. Some studies excluded people with OA, some only excluded if they had advanced OA and some did not exclude OA.

Some meta-analyses explicitly excluded studies if the procedure was augmented with other substances. It is likely some meta-analyses excluded studies if they did not indicate that bone marrow stimulation happened. More detail is in the procedure details section.

The evidence includes research done in many countries; it is likely that only 3 studies had data from a single country. No study included evidence mostly or entirely from the UK. The network meta-analysis only included level 1 or 2 comparative evidence (Miglionini 2021a), but the other meta-analyses included studies with other research designs.

More men or males than women or females were included in most of the studies and most reported mean lesion size was between 3.0 and 4.0 cm^2. Kim (2020b) reported that 67% of people were female. The mean lesion size was between 4.0 and 4.7 cm^2. In the RCT follow-up study by Shive (2015), the mean lesion size was between 2.1 and 2.4 cm^2.

Follow up was 2 years in 3 of the RCTs (Altschuler 2023, Kim 2020b, Kon 2018), 100 months in the RCT of 24 people (de Girolamo 2019), 5 years in the RCT follow-up study (Shive 2015) and up to 7 years in the registry study (Gille 2021). Mean follow up was about 3 years in the meta-analyses; da Cunha (2020) reported a maximum follow up of 84 months. Table 2 presents study details.

Figure 1 Flow chart of study selection

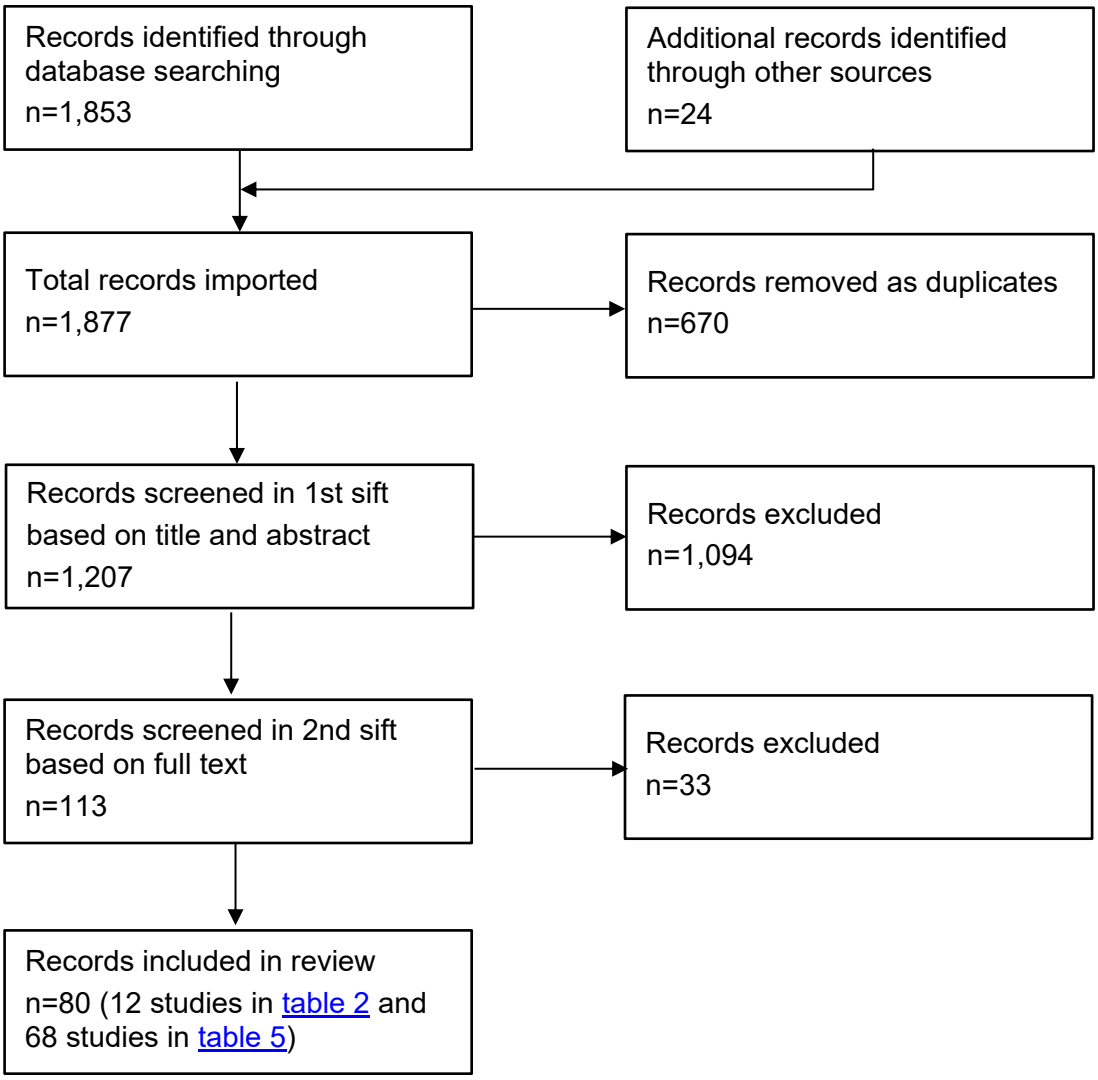

Table 2 Study details

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
1	Migliorini, 2022a The countries where the included studies were done was not reported. The search strategy included studies written in English, German, Italian, French and Spanish.	n=548 people in 18 studies 67% male; 33% female Mean defect size 3.2 cm^2 (SD 1) Mean BMI 27 kg per m^2 (SD 1.3)	Mean 27 (SD 6)	Systematic review and meta-analysis comparing microfracture and scaffold with microfracture for focal chondral knee defects. Searches were done in January 2022.	Peer-reviewed publications of level 1 to 4 clinical trials investigating microfracture with scaffold or microfracture with scaffold compared with microfracture for focal chondral defects in the knee. Studies reporting findings from lesions in multiple locations or kissing lesions, or data on revision settings were excluded, as well as studies with missing data in the outcomes of interest.	Microfracture with scaffold compared with microfracture alone (technologies in the scaffold arm were mixed although their names were not reported). Rehabilitation protocols of the included studies were not reported.	Mean 40 months (SD 27 months)
2	Kim, 2020a	n=966 knees in 29 studies	Mean in the microfracture	Systematic review and meta-analysis	Studies that included people who had	Microfracture with scaffold (Chondro-Gide,	Mean follow up in the scaffold

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
	The countries where the included studies were done was not reported.	Aggregate males: females was not reported Mean lesion size in the scaffold group 3.5 cm^2, mean lesion size in the microfracture only group 3.3 cm^2	with scaffold group 36.1 Mean in the microfracture only group 35.7	comparing microfracture with scaffold with microfracture only for cartilage repair in the knee after a minimum of 2 years of follow up. Searches were done in June 2019.	microfracture with scaffold or microfracture alone for cartilage defect in the knee and reported clinical or cartilage repair outcomes at 2 or more years of follow up were eligible. Studies were excluded if outcome reporting was incomplete, if people had concomitant high tibial osteotomy or greater than 10-year follow up.	Geistlich Pharma AG; Chondrotissue, BioTissue AG) compared with microfracture. Mixed rehabilitation protocols were reported in Table 2 of the publication. The authors did not comment on the effect of this on the findings.	group 38 months Mean follow up in the microfracture only group 53 months
3	Migliorini, 2022b The countries where the included studies	n=1,667 people in 47 studies 64% men; 36% women	Mean 35 (SD 7)	Systematic review and meta-analysis of studies comparing microfracture with scaffold with mACI.	Level 1 to 4 studies reporting the findings of microfracture with scaffold and or mACI procedures for chondral knee defects, with a minimum of 5	Microfracture with scaffold (n=15 studies, 373 people) compared with mACI (n=32 studies, 1,237 people).	Mean 38 (SD 22) months

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
	were done was not reported. The search strategy included studies written in English, German, Italian, French and Spanish.	Mean defect size 3.9 cm^2 (SD 1.2) Mean BMI 25.5 kg per m^2 (SD 1.6)		Searches were done in January 2022.	people and which used a cell-free bioresorbable membrane. Studies that augmented the procedure with bone marrow concentrate, mesenchymal stem cells or growth factors were excluded. Studies including people with kissing lesions or end-stage OA were excluded. Studies also had to report the length of follow up and data for the outcomes of interest.	Rehabilitation protocols of the included studies were not described.	
4	Migliorini, 2021a	n=2,210 people in 36 studies	Median 33.9 (range 30 to 37)	Systematic review and Bayesian network meta-analysis	Prospective level 1 or 2 clinical evidence comparing 2 or more	The following were compared with one another: microfracture with scaffold	Median 36 months (IQR 24 to 60)

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
	The countries where the included studies were done was not reported. The search strategy included studies written in English, German, Italian, French and Spanish.	64% male; 36% female Mean defect size 3.7 cm^2 (SD 1.2) Median BMI 25.3 kg per m^2		comparing surgical strategies for managing chondral knee defects. Searches were done in July 2021.	interventions for chondral knee defects, with at least 12 months of follow up. Studies were excluded if they included people with end-stage OA or kissing lesions, or if data were missing in the outcomes of interest. Procedures augmented with less committed cells (for example, mesenchymal stem cells) were not considered.	(n=5 studies with 103 people), microfracture alone, OAT, ACI, mACI alone. The study reported that a mixture of scaffold technologies were included. Rehabilitation protocols were not reported or commented on.	
5	Tan, 2023 Included studies were done in Belgium, Singapore, Germany,	n=609 people in 24 studies 62% male; 38% female	Arthroscopic group mean 38 Open surgery group mean 34	Systematic review and meta-analysis of studies investigating the procedure by open or arthroscopic	Clinical studies (RCT, cohort, case control or case series) in adults with tibiofemoral or patellofemoral lesions grade 3	This study compares the open surgery approach (n=18 studies) with the arthroscopic approach (n=5 studies).	Arthroscopic group mean 38 months; open surgery group mean 52 months

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
	Italy, Romania, Brazil, Poland, France and Norway.	Mean lesion size 3cm^2 in both groups Mean BMI 27 kg per m^2 in the open surgery group; 26 kg per m^2 in the arthroscopic group		technique. Searches were done in October 2022.	and above. All studies had to include people having the procedure with either open or arthroscopic approach. Studies with incomplete information or with people who had other surgical management, were excluded.	Scaffolds included BioTissue, Chondrotissue, Chondro-Gide, Hyalofast and CartiFill. Rehabilitation protocols were not reported or commented on.	
6	da Cunha, 2020 Countries of the included studies were not reported.	n=331 people in 10 studies 56% male; 44% female Mean defect size=3.2 cm^2 Weighted mean BMI=25.2 kg per m^2	Mean 37	Systematic review and meta-analysis of studies of enhanced microfracture with acellular scaffolds.	Peer-reviewed publications with at least 5 people. Studies had to assess the outcomes of cell-free matrices to primarily treat tibiofemoral full or partial thickness focal defects in skeletally mature people at a minimum of 12 months. Studies	Enhanced microfracture with acellular scaffolds (including BST-CarGel, Chondro-Gide, Hyalofast, ChonDux, CartiFill and Chondrotissue) Rehabilitation protocols were	Range 12 to 84 months

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
					including people with degenerative, musculoskeletal disorders or inflammatory disease including OA, or having concomitant cartilage surgery, or surgery on multiple lesions, or reoperations were excluded.	not reported but the authors commented that this was heterogeneous.	
7	Altschuler, 2023 26 centres across the US, Belgium, Hungary, Israel, Italy, Poland, Romania and Serbia	n=251 (n=167 in scaffold arm; n=84 surgical standard of care arm) 64% and 61% male; 36% and 39% female in the scaffold and surgical standard of care arms, respectively. 59% and 49% had lesions bigger than	Scaffold arm: Mean 42 (SD 11) Surgical standard of care arm: mean 46 (SD 11)	2-arm multicentre RCT with 2:1 randomisation ratio. Recruitment was between September 2017 and November 2019.	People aged 21 to 75 with up to 3 joint surface lesions (grade 3a or above), or on the femoral chondyle or trochlea with total area 1 to 7 cm^2. People were excluded if: their KOOS pain subscale rating was less than 20 (low) or more than 65 (high), their	Scaffold (Agili-C, Cartiheal Ltd; press-fit into a hole drilled into the subchondral bone) compared with surgical standard of care (arthroscopic debridement, microfracture). Rehabilitation protocol involved partial weightbearing for	24 months

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
		3 cm^2 in the scaffold and surgical standard of care arms, respectively. Mean BMI 26.4 and 27.9 kg per m^2 in the scaffold and surgical standard of care arms, respectively			defect was more than 8 mm deep into the bone, their lesions were in the tibia or patella and grade 4a or higher, they had severe OA or significant instability or lack of remaining meniscus in the index knee, or if the lesion was uncontained, or if the implant could not be positioned with a 2 mm recess of articular cartilage.	4 weeks, building to full weightbearing at 6 weeks. Isometric exercises with electrostimulation immediately after surgery. Cryotherapy with passive motion device for up to 3 weeks. Stationary cycling when knee flexion reached 100 degrees. At about 2 months, most people were advised to use full range of motion. Strengthening training at 3 months.	
8	Kim, 2020b	n=100 (n=52 scaffold group:	Mean 49 and 52 in the scaffold and	2-arm multicentre	People aged 15 to 65 with knee cartilage defects,	Atelocollagen gel scaffold applied after	24 months

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
	10 hospitals in South Korea	n=48 microfracture alone) 33% male; 67% female (out of 99) Mean lesion size 4.0 cm^2 and 4.7 cm^2 in the scaffold and microfracture groups, respectively. Mean BMI 25 kg per m^2 in both arms	microfracture groups, respectively	RCT with 1:1 allocation. Enrolment began in 2013 and the last follow up was in September 2018.	misalignment of the tibia and femur or treatment for the misalignment. People were excluded if they had contraindications for the scaffold or glue (history of an autoimmune disease or anaphylactic reaction, sensitivity to transplant or porcine protein, were pregnant or lactating) or previous ligament surgery.	microfracture, with thrombin and fibrinogen (authors called this collagen-augmented chondrogenesis technique using CartiFill, Sewon Cellontech, Seoul, Korea) compared with microfracture alone. Rehabilitation programme included range of motion daily exercises from day 1. Toe touch ambulation only for up to 4 weeks. Full weightbearing from 6 weeks.	
9	Kon, 2018	n=100 completed the study (n=51	Mean 34 and 35 in the	2-arm multicentre	People with chondral or	Bioceramic composite	2 years

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
	Italy, Sweden, Belgium, Switzerland, Austria, Germany, Norway, Poland and South Africa	scaffold; n=49 bone marrow stimulation) 71% and 63% male: 29% and 37% female in the scaffold and bone marrow stimulation groups, respectively. Mean lesion size 3.4 cm^2 and 3.5 cm^2 in the scaffold and bone marrow stimulation groups, respectively. Mean BMI 26 and 25 kg per m^2 in the scaffold and bone marrow stimulation groups, respectively	scaffold and bone marrow stimulation groups, respectively.	RCT with 1:1 allocation. Recruitment was between 2011 and 2013.	osteochondral lesions in the knee.	scaffold (MaioRegen, Fin-Ceramica Faenza S.p.A., Italy; press-fit into a hole drilled into the subchondral) compared with bone marrow stimulation. Isometric and isotonic exercises from discharge with electrical neuromuscular stimulation. Weightbearing with crutches at week 4 working toward full weightbearing. Swimming and cycling from week 4 and low active functional	

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
						training from 4 to 6 months. Joint impact activities from 1 year.	
10	Shive, 2015 26 clinical sites across Canada, Spain and South Korea	n=60 (n=34 scaffold group; n=26 microfracture) 65% and 54% male: 35% and 46% femalein the scaffold and microfracture groups, respectively. Mean lesion size 2.4 cm^2 and 2.1 cm^2 in the scaffold and microfracture groups, respectively. Mean BMI 27.6 kg per m^2 and 25.7 kg per m^2 in the scaffold and	Mean 34 and 40 in the scaffold and microfracture groups, respectively	Extended follow-up phase from a 2-arm multicentre RCT with 1:1 allocation. Enrolment to the original RCT began in 2006 and last follow up of the extended study was in February 2014.	People were recruited from the original pool of RCT participants. People were aged 18 to 55 with a single, focal cartilage lesion on the femoral chondyles and had moderate pain (greater than 4 points on the VAS) on entry to the RCT.	Microfracture plus gel scaffold containing chitosan (BST-CarGel, Piramal Life Sciences, Bio-Orthopaedic Division) compared with microfracture alone. Rehabilitation included 6 weeks of no weightbearing and full weight bearing at 8 weeks. Up to 32 physiotherapy sessions over 8 weeks with assisted passive motion. Full	5 years

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
		microfracture groups, respectively				impact activity after 12 months.	
11	Gille, 2021 This was a multicentre study in Germany	n=131 80 males; 48 females Mean lesion size 3.4 cm^2 in males and 3.2 cm^2 in females Mean BMI=26 kg per m^2	Mean 36 in males and 37 in females	Follow up of a previously published multicentre registry study (people enrolled in the 'AMIC registry' between 2003 and 2013). The earlier publications of short and mid-term data were included in the overview when this topic was first assessed by the committee.	People with symptomatic, circumscribed grade 3 or 4 lesions. People were excluded if they had concomitant surgery, advanced OA, significant narrowing of the joint lines, underlying rheumatic disease, total meniscectomy, BMI more than 30, or deviation of the mechanical axis of the affected compartment.	Microfracture and collagen scaffold (Chondro-Gide, Geistlich Pharma) The rehabilitation protocol was not described.	Mean 4.6 years (up to 7 years)

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
12	de Girolamo, 2019 Italy	n=24 (n=12 scaffold with bone marrow aspirate concentrate, n=12 scaffold only) 58% and 67% male: 42% and 33% female in the scaffold and scaffold with bone marrow aspirate concentrate groups, respectively. Mean lesion size 3.8 and 3.4 cm^2 in the scaffold and scaffold with bone marrow aspirate concentrate groups, respectively	Mean 30 in both groups.	2-arm single centre RCT with 1:1 allocation. Recruitment was between December 2007 and February 2010.	People aged between 18 and 55 with 1 or 2 grade 3 or 4 tibiofemoral or patellofemoral lesions between 2 and 8 cm^2 and with normal surrounding cartilage. People with immunomediated knee pathologies, serious cardiac pathologies or other general conditions were excluded.	Microfracture and collagen scaffold group (Chondro-Gide, Geistlich Pharma AG) compared with a microfracture, collagen scaffold (Chondro-Gide, Geistlich Pharma AG) and bone marrow aspirate concentrate group. Rehabilitation protocol was the same for both groups: for condylar chondral defect, immediate full range of motion without any weightbearing for 3 weeks, then full bearing after 6 weeks; for	100 months

Study no.	First author, date country	Patient characteristics	Age (years)	Study design	Inclusion criteria	Intervention	Follow up
						patellar defects, progressively restore full range of motion and bearing within a few days. All were advised to return to sports 4 to 6 months after surgery.	

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Migliorini, 2022a	**IKDC (subjective)** • The authors cite a MCID (the smallest difference on the scale that is considered to represent clinically meaningful change) of 15 out of 100 points for this scale. • Compared with baseline (mean follow up 40 months), people who had the scaffold procedure had a statistically significant mean increase of 34 points (out of 100, 95% CI 33 to 35, p<0.001) on the IKDC score.	**Surgical failure rate** The failure rate for people who had the scaffold procedure was 3.8% (9 out of 236 people). **Revision rate** The revision rate for people who had the scaffold procedure was 4.5% (9 out of 210 people) at a mean of 43.6 months. Meta-analysis showed the OR for

First author, date	Efficacy outcomes	Safety outcomes
	• Compared with microfracture (n=3 studies, mean follow up 40 months), people who had the scaffold procedure had a statistically significantly greater IKDC score than people who had microfracture. The weighted mean difference between groups was 11.8 points (95% CI 6.7 to 17.0, p<0.001). **VAS (pain)** • The authors cite a MCID of 2.7 out of 10 points for this scale. • Compared with baseline (mean follow up 40 months), people who had the scaffold procedure had a statistically significant mean decrease of 3.9 points (out of 10, 95% CI -3.7 to -4.10, p<0.001) on the VAS scale. • Compared with microfracture (n=3 studies, mean follow up 40 months), people who had the scaffold procedure had a statistically significantly lower VAS score than people who had microfracture. The weighted mean difference between groups was -1.0 points (95% CI -0.05 to -2.0, p=0.04). **Lysholm score** • The authors cite a MCID of 10 out of 100 points for this scale. • Compared with baseline (mean follow up 40 months), people who had the scaffold procedure had a	revision surgery favoured AMIC, 0.16 (95% CI 0.06 to 0.44, p<0.001, n=6 studies). **Hypertrophy** At last follow up, no people who had the scaffold procedure had signs of hypertrophy.

First author, date	Efficacy outcomes	Safety outcomes
	statistically significant mean increase of 28 points (out of 100, 95% CI 26.9 to 29.1, p<0.001) on the Lysholm score. **Tegner score** • The authors cite a MCID of 0.5 out of 10 points for this scale. • Compared with baseline (mean follow up 40 months), people who had the scaffold procedure had a statistically significant mean increase of 0.8 points (out of 10, 95% CI 0.7 to 0.9, p=0.03) on the Tegner scale.	
Kim, 2020a	**IKDC (subjective)** After a minimum of 2 years, improvements in IKDC scores were statistically significantly larger in the scaffold group than the microfracture group (p<0.001): • Scaffold group mean improvement 45.9 (out of 100, 95% CI 36.2 to 55.5, 4 studies) • Microfracture mean 27.2 (out of 100, 95% CI 23.3 to 31.1, 5 studies) **VAS (pain)** After a minimum of 2 years, improvements in VAS scores were not statistically significantly larger in the scaffold group than the microfracture group (p=0.06): • Scaffold group mean improvement 4.8 (out of 10, 95% CI 4.2 to 5.5, 7 studies)	Safety outcomes were not reported in this systematic review and meta-analysis.

First author, date	Efficacy outcomes	Safety outcomes
	• Microfracture mean 3.2 (out of 10, 95% CI 1.6 to 4.8, 5 studies) **Lysholm score** After a minimum of 2 years, improvements in Lysholm scores were not statistically significantly larger in the scaffold group than the microfracture group (p=0.38): • Scaffold group mean improvement 33.3 (out of 100, 95% CI 28.3 to 38.2, 7 studies) • Microfracture mean 30.1 (out of 100, 95% CI 25.3 to 35.0, 9 studies) **Tegner score** After a minimum of 2 years, improvements in Tegner scores were not statistically significantly larger in the scaffold group than the microfracture group (p=0.37): • Scaffold group mean improvement 1.0 (out of 10, 95% CI 0.8 to 1.3, 4 studies) • Microfracture mean 1.4 (out of 10, 95% CI 0.6 to 2.1, 5 studies) **MOCART** After a minimum of 2 years, overall MOCART scores were statistically significantly better in the scaffold group than the microfracture group (p=0.005):	

First author, date	Efficacy outcomes	Safety outcomes
	• Scaffold group mean 69.3 (out of 100, 95% CI 55.1 to 83.5, 5 studies) • Microfracture mean 41.0 (out of 100, 95% CI 27.3 to 54.7, 4 studies) **Defect filling rate** After a minimum of 2 years, defect filling rate was statistically significantly better in the AMIC group than the microfracture group (OR 1.58, 95% CI, 1.07 to 2.33, p=0.008): • AMIC mean 77.3% (95% CI 66.7 to 87.9, 9 studies) • Microfracture mean 47.9% (95% CI 29.2 to 66.7, 9 studies)	
Migliorini, 2022b	Results were summarised from 47 studies including 1,667 people with collective mean follow up of 38 months (SD 22). **IKDC (subjective)** People who had the microfracture with scaffold procedure had a statistically significantly higher mean IKDC score than people who had mACI (MD 7.7, p=0.03): • microfracture with scaffold mean 79.2 (SD 10.4) • mACI mean 71.5 (SD 6.3) **VAS (pain)** There was no statistically significant difference in VAS scores between people who had the microfracture with scaffold procedure and mACI (MD 0.07, p=0.5, not significant):	**Surgical failure rate** There was a statistically significant difference in failure rate between people who had the microfracture with scaffold procedure and people who had mACI (OR 0.2, 95% CI 0.0 to 0.9, p=0.04): • microfracture with scaffold rate 1.8 (2 of 114 observations) • mACI rate 7.3 (41 of 562 people) **Revision rate** The OR for revision rate between people who had the microfracture with scaffold procedure and people who had mACI was 0.5 (95% CI 0.2 to 1.0, p=0.07):

First author, date	Efficacy outcomes	Safety outcomes
	• microfracture with scaffold mean 2.8 (SD 2.2) • mACI mean 2.9 (SD 1.3) **Lysholm score** People who had the microfracture with scaffold procedure had a statistically significantly higher mean Lysholm score than people who had mACI (MD 16.1, p=0.02): • microfracture with scaffold mean 81.9 (SD 7.1) • mACI mean 65.7 (SD 28.2) **Tegner score** There was no statistically significant difference in Tegner scores between people who had the microfracture with scaffold procedure and mACI (MD 0.3, p=0.2, not significant): • microfracture with scaffold mean 4.4 (SD 0.6) • mACI mean 4.7 (SD 0.8)	• microfracture with scaffold rate 6 (7 of 117 observations) • mACI rate 11.9 (39 of 328 observations) **Hypertrophy** The OR for hypertrophy rate between people who had the microfracture with scaffold procedure and people who had mACI was 0.1 (95% CI 0.0 to 1.0, p=0.05): • microfracture with scaffold rate 0 (0 of 96 observations) • mACI rate 7.6 (29 of 381 observations) **Knee arthroplasty** There was no statistically significant difference in the knee arthroplasty rate between people who had the microfracture with scaffold procedure and people who had mACI (OR 0.5, 95% CI 0.0 to 3.6, p=0.4): • microfracture with scaffold rate 1.6 (2 of 126 observations) • mACI rate 3.1 (2 of 64 observations)
Migliorini, 2021a	**Lysholm score (median follow up 3 years)** Compared with microfracture, ACI, mACI and OAT, the network meta-analysis found the procedure had a higher Lysholm score (SMD 4.0, 95% CI -10 to 18).	**Surgical failure rate** The procedure had the lowest failure rate compared with microfracture, ACI, mACI and OAT (log OR 0.2, 95% CI -2.0 to 1.7).

First author, date	Efficacy outcomes	Safety outcomes
	Tegner score (median follow up 3 years) Compared with microfracture, ACI, mACI and OAT, the network meta-analysis found the procedure had a higher Tegner score (SMD-2.1, 95% CI -3.2 to -1.0). Tests of heterogeneity precluded network meta-analysis of the IKDC scores.	**Revision surgery** The procedure had the lowest revision surgery rate compared with microfracture, ACI, mACI and OAT (log OR 0.9, 95% CI -0.8 to 2.6). **Hypertrophy** Microfracture had the lowest rate of hypertrophy (log OR -0.2, 95% CI -3.0 to 2.7). The procedure had the second lowest rate of hypertrophy (log OR 0.2, 95% CI -1.4 to 1.8).
Tan, 2023	Mean follow up was 51 months across the 24 studies included in this meta-analysis. **KOOS** There was no statistically significant difference in KOOS score at the last follow up between the open and the arthroscopic groups (mean difference 8.1, 95% CI -4.0 to 20.1, p=0.19). Both groups had statistically significant improvements from baseline: • Open surgery mean improvement 27.9 (95% CI 22.2 to 33.7, p<0.001, 8 studies) • Arthroscopic mean improvement 36.1 (95% CI 27.9 to 44.3, p<0.001, 3 studies) **IKDC (subjective)** There was no statistically significant difference in IKDC score at the last follow up between the open surgery group and	**Failure** 3 open surgery studies reported that treatment failed in 11 people. **Revision surgery** 1 arthroscopic study reported whether there was any revision surgery. The revision rate was zero in this study. 10 open surgery studies reported whether there was any revision surgery. A total of 32 people had revision surgery (denominator not reported). Not all of these were related to the procedure. **Infection** 2 arthroscopic and 4 open surgery studies reported whether there were any infections. None of these studies reported infections.

First author, date	Efficacy outcomes	Safety outcomes
	arthroscopic group (mean difference 3.2, 95% CI -2.7 to 9.1, p=0.29). Both groups had statistically significant improvements from baseline: • Open surgery mean improvement 39.6 (95% CI 30.8 to 48.5, p<0.001, n=6 studies) • Arthroscopic mean improvement 34.0 (95% CI 22.5 to 45.5, p<0.001, n=4 studies) **VAS (pain)** There was a statistically significant difference in VAS score at the last follow up, favouring the arthroscopic group over the open surgery group (mean difference-6.6, 95% CI -1.8 to -11.4, p=0.007). Both groups had statistically significant improvements from baseline: • Open surgery mean improvement -3.8 (95% CI -3.0 to -4.5, p<0.001, n=12 studies) • Arthroscopic mean improvement -4.1 (95% CI -3.1 to -5.1, p<0.001, n=3 studies) **MOCART** • Open surgery mean MOCART score 64.59 (95% CI 57.4 to 71.8, n=6 studies) • Arthroscopic mean score 58.3 (95% CI 50.5 to 66.1, n=1 study)	**Deep vein thrombosis** 1 arthroscopic study reported that 3 people had deep vein thrombosis. In 2 open surgery studies that reported it, there were no deep vein thrombosis events. **Knee stiffness** 1 arthroscopic study reported no knee stiffness events. 1 open surgery study reported 1 person had knee stiffness. **Arthroplasty** 4 studies reported that 5 people had arthroplasty.

First author, date	Efficacy outcomes	Safety outcomes
da Cunha, 2020	**IKDC (subjective)** At a median follow up of 24 months (range 12 to 84), weighted mean improvement in IKDC score 33.2 (SD 10.2, n=116). **VAS (pain)** At a median follow up of 24.4 months (range 12 to 30 months), weighted mean decrease in VAS score 4.2 (SD 0.8, n=164). **Imaging outcomes** Findings varied by scaffold used and when more than 1 study reported findings for the same technology, the results also tended to vary. Overall, defect filling ranged from 19% to 'complete'.	**Overall adverse event rates** Seven of 10 studies reported whether there were treatment-related adverse events, including 3 studies that reported there were none. In 1 study, 13 people in the scaffold arm (19%) reported an adverse event, compared with 18 people (27%) in the microfracture arm; more than 90% were mild or moderate in both arms. In 1 study of 18 people, 78% reported mild or moderate adverse events (n=39 events). **Knee pain** In 1 study, the most common event was knee pain (11%). In 1 study, 1 person had persistent pain and early degenerative changes of the knee joint. In 1 study, 44% of adverse events were pain and swelling and 50% joint pain. Two events were likely or definitely device-related and classified as mild. **Infection** In 1 study, cellulitis was reported in 1 person. **Haematoma** In 1 study, 1 person developed haematoma.

First author, date	Efficacy outcomes	Safety outcomes
		Knee stiffness In 1 study, 45% (9 people) needed mobilisation under anaesthesia for knee stiffness.
Altschuler, 2023	**KOOS (n=164 scaffold, n=83 surgical standard of care)** The scaffold group had statistically significant greater mean improvements in KOOS score compared with the surgical standard of care group at all timepoints: • Mean difference in improvement between groups at 6 months 8.2 (95% CI 3.3 to 13.0, p=0.001) • Mean difference in improvement between groups at 12 months 12.5 (95% CI 7.3 to 17.8, p<0.001) • Mean difference in improvement between groups at 18 months 18.3 (95% CI 13.0 to 23.5, p<0.001) • Mean difference in improvement between groups at 24 months (primary outcome) 22.5 (95% CI 17.0 to 28.0, p<0.001) All secondary endpoints (subscales of KOOS including pain, quality of life, ADL and responder rate [change of 30 points or more] at 24 months) were considered statistically superior in the scaffold group compared with the surgical standard of care group (posterior probability of superiority 1). This was robust to worst-case sensitivity analysis. **IKDC (subjective)** At 12 months, the authors cite an MCID of 16.7 points. Mean change in IKDC scores was greater than the MCID at 6, 12,	**Revision surgery because of OA progression** No people (of 167) in the scaffold group had revision surgery because of OA progression; 4.8% (4 out of 84) people in the surgical standard of care group had revision surgery because of OA progression. **Surgical failure rate** There were more treatment failures in the surgical standard of care group than the scaffold group (p=0.002): • 7.2% (n=12 people) in the scaffold group • 21.4% (n=18 people) in the surgical standard of care group • Higher failure rates were seen in the surgical standard of care group in people who had larger lesions or OA. This pattern was not seen in the scaffold group. **Serious adverse events** **Wound complications** 1.2% (2 out of 167) of people in the scaffold group and 1.2% (1 out of 84) in the standard of care group

First author, date	Efficacy outcomes	Safety outcomes
	18 and 24 months, and the difference between the scaffold and surgical standard of care groups was statistically significant at all timepoints. At 6 months: • Scaffold group mean IKDC score 24.0 (SD 18.8) • Difference between groups was not reported. At 12 months: • Scaffold group mean IKDC score 32.5 (SD 20.6) • Difference between groups 12.0 (95% CI, 6.5 to 17.5, p<0.001) At 18 months: • Scaffold group mean IKDC score 38.1 (SD 20.8) • Difference between groups 16.3 (95% CI 10.7 to 21.9, p<0.001) At 24 months: • Scaffold group mean IKDC score 43.0 (SD 21.2) • Difference between groups 22.7 (95% CI 16.8 to 28.6, p<0.001) **Defect filling (n=156 scaffold, n=68 surgical standard of care)** At 24 months, 88.5% of the scaffold group had 75.0% or more defect fill compared with 30.9% in the surgical standard of care group (p<0.001).	had wound complications requiring antibiotics and prolonged dressing. **Septic arthritis** 1 person in the scaffold group had septic arthritis. The implant was removed followed by surgical debridement and antibiotics. **Decreased range of motion** 1.2% (2 out of 167 people) in the scaffold group had decreased range of motion in the index knee compared with baseline. **Muscle atrophy** 1.2% (2 out of 167 people) in the scaffold group had muscle atrophy that persisted at last follow up. **Deep vein thrombosis** 1 person in each group had deep vein thrombosis, which was managed pharmacologically. **Other adverse events** **Transient knee pain** Transient knee pain was the most common adverse event, seen in 15.0% of the scaffold group compared with 39.3% of the surgical standard of care group. **Swelling and effusion** 5.4% in the scaffold group compared with 4.8% in the surgical standard of care group.

First author, date	Efficacy outcomes	Safety outcomes
	At 24 months, 1.3% of the scaffold group had less than 50% defect fill compared with 50% in the surgical standard of care group. **Covariate analyses** The effects of OA, age and lesion size were explored as covariates in this study. The difference between treatment groups in KOOS improvement at 24 months was not statistically different by OA (none compared with mild to moderate OA, p=0.48) or age (aged less than 50 compared with 50 or older, p=0.54). The difference between treatment groups in KOOS improvement at 24 months showed statistically significant variance by lesion size. People with lesions greater than 3 cm^2 had more improvement than people with smaller lesions (p not reported).	**Overall adverse event rate** There were fewer adverse events in the scaffold group (58.7%, 98 out of 167 people had 1 or more adverse events) compared with the surgical standard of care group (77.4%, 65 out of 84 people had 1 or more adverse events). The authors note that these rates included unrelated events and the trial was done during the COVID-19 pandemic.
Kim, 2020b	**KOOS (n=45 scaffold, n=44 microfracture only)** Overall KOOS was statistically significantly improved compared with baseline within the scaffold and microfracture groups at 12 and 24 months, but not statistically significantly different between the groups at either timepoint: • At 12 months, the scaffold group mean KOOS 69.7 (SD 16.4) and the microfracture group mean KOOS 70.3 (SD 17.6, p=0.95)	**Overall adverse event rates** No adverse events were categorised as related to the scaffold or microfracture surgery. • 4 serious adverse events were recorded (2 in each arm). None were classed as related to the procedure. In the scaffold arm, 1 person had a urethral caruncle removed 3 months postoperatively and 1 person had acute hepatoma 2 months postoperatively.

First author, date	Efficacy outcomes	Safety outcomes
	• At 24 months, the scaffold group mean KOOS 77.1 (SD 14.1) and the microfracture group mean KOOS 75.2 (SD 15.5, p=0.69) • At 24 months, the rate of scores equal to or more than the MCID of 16.7 points was not statistically different between groups (p=0.94) All subscales showed statistically significant improvements within both groups for the improvement in scores between baseline and 12 months and baseline and 24 months except for the sport and recreation subscale for the microfracture-only group at 12 months (p=0.06). **IKDC (subjective)** Overall IKDC was statistically significantly improved compared with baseline within the scaffold and microfracture groups at 12 and 24 months, but not statistically different between the groups at either timepoint: • At 12 months, the scaffold group mean IKDC 65.8 (SD 19.3) and the microfracture group mean IKDC 65.8 (SD 21.2, p=0.998) • At 24 months, the scaffold group mean IKDC 70.3 (SD 18.5) and the microfracture group mean IKDC 71.2 (SD 19.9, p=0.63) There were no statistically significant differences in IKDC score between groups at 12 or 24 months.	• In the microfracture only arm, 1 person had metal removed from the left distal tibia 9 months after surgery and 1 person had unexpected hospitalisation because of left knee pain and swelling 2 months postoperatively.

First author, date	Efficacy outcomes	Safety outcomes
	All subscales showed statistically significant improvements within both groups for the improvement in scores between baseline and 12 months and baseline and 24 months. **VAS (pain)** Note this study used a 0- to 100-point VAS scale in which 0 is worst pain and 100 is no pain. There was no statistically significant difference in VAS scores at any timepoint between the groups. • At 12 months, the scaffold group mean VAS 22.2 (SD 24.1) and the microfracture-only group 21.0 (SD 20.7, p=0.94) • At 24 months, the scaffold group mean VAS 15.5 (SD 21.6) and the microfracture-only group 21.5 (SD 25.9, p=0.43) • At 24 months, there were more people in the scaffold group (42.7%) than the microfracture-only group (32.6%) with a MCID compared with baseline on the VAS scale (OR 2.81, 95% CI 1.01 to 7.78, p=0.047). **MOCART (n=42 scaffold, n=40 microfracture only)** Total MOCART score at 12 months was not statistically different between the scaffold group (mean 50.9, SD 19.8) and microfracture group (mean 45.7, SD 19.9, p=0.23). Three subscales of MOCART at 12 months favoured the scaffold group: degree of defect repair and filling, integration	

First author, date	Efficacy outcomes	Safety outcomes
	with the border zone and effusion (p=0.02, p=0.006 and p=0.008, respectively). **Defect filling** At 12 months, 50% or higher defect filling was seen in 41.6% of the scaffold group and 29.2% of the microfracture group (OR 4.0, 95% CI 1.3 to 12.4, p=0.01).	
Kon, 2018	**KOOS** Exact values for KOOS outcomes were not reported. Both the scaffold and bone marrow stimulation-only groups had statistically significant improvements from baseline to 2 years postoperatively. There were no statistically significant differences between groups (p value not reported). **IKDC (subjective)** Both the scaffold and bone marrow stimulation-only groups had statistically significant improvements from baseline to 2 years postoperatively (p value not reported). There were no statistically significant differences between groups (p value not reported): • In the scaffold group, mean IKDC subjective 43.2 (SD 16.6) at baseline, 60.7 (SD 17.3) at 1 year and 66.7 (SD 21.0) at 2 years. • In the bone marrow stimulation group, mean IKDC subjective 41.1 (SD 15.9) at baseline, 61.8 (SD 18.0) at 1 year and 63.6 (SD 18.2) at 2 years.	**Overall adverse event rate** There were 13 adverse events and 3 serious adverse events related to the procedure in the scaffold group compared with 4 adverse events and 1 serious adverse event in the bone marrow stimulation group. **Failures** There were 2 surgical failures in the scaffold group and none in the bone marrow stimulation group. **Minor early postoperative symptoms** There were 8 events in the scaffold group and 3 in the bone marrow stimulation group. **Inflammation** There were 3 inflammation events in the scaffold group and none in the bone marrow stimulation group.

First author, date	Efficacy outcomes	Safety outcomes
	• Adjusted mean difference between groups -0.48 (not significant). • A subgroup analysis found the difference was statistically significantly different between treatment groups in people with deep osteochondral lesions (p=0.04) and sports active people (p=0.03), favouring the scaffold group. **VAS (pain)** Both the scaffold and bone marrow stimulation-only groups had statistically significant improvements from baseline to 2 years postoperatively (p value not reported). There were no statistically significant differences between groups (p value not reported): • In the scaffold group, mean VAS 50.1 (SD 26.7) at baseline, 23.8 (SD 20.8) at 1 year and 26.5 (SD 27.5) at 2 years. • In the bone marrow stimulation group, mean VAS 53.1 (SD 22.7) at baseline, 29.2 (SD 23.2) at 1 year and 23.2 (SD 20.9) at 2 years. • Adjusted mean difference between groups=6.6 (not significant). **Tegner score** Both the scaffold and bone marrow stimulation-only groups had statistically significant improvements from baseline to 2 years postoperatively (p value not reported). There were no	**Joint adhesions** There were 2 serious and 1 non-serious joint adhesion events in the scaffold group and none in the bone marrow stimulation group. **Persistent pain** There was 1 serious and 1 non-serious persistent pain event in the scaffold group and none in the bone marrow stimulation group. **Loose body** There was 1 loose body recorded in the bone marrow stimulation arm and none in the scaffold arm.

First author, date	Efficacy outcomes	Safety outcomes
	statistically significant differences between groups (p value not reported): • In the scaffold group, median Tegner 3 (range 0 to 7) at baseline, 4 (range 2 to 7) at 1 year and 4 (range 1 to 9) at 2 years. • In the bone marrow stimulation group, median Tegner 3 (range 0 to 9) at baseline, 4 (range 1 to 9) at 1 year and 4 (range 2 to 8) at 2 years. • Adjusted mean difference between groups 0.14 (not significant). **IKDC (objective)** The percentage of people assessed as having 'normal' or 'nearly normal' knees increased from baseline to 2 years of follow up in the scaffold group. They did not report if this was statistically significant. The scores also increased in the bone marrow stimulation group but the authors reported this was not statistically significant (p value not reported). There was no statistically significant difference between groups (p value not reported). **MOCART** There was no statistically significant difference between groups. **Covariate analyses**	

First author, date	Efficacy outcomes	Safety outcomes
	In the scaffold group, people with grade 4 lesions and who did not have concomitant anterior cruciate ligament surgery had better IKDC outcomes ($p<0.05$). Outcomes did not statistically significantly vary by age, sex or lesion size in this group. A subgroup of people with deep lesions involving the subchondral bone who did not have anterior cruciate ligament surgery were analysed for between group differences. From baseline to 2 years, people who fit this criterion and had the scaffold procedure (n=27) had more improvement on the IKDC subjective score at 2 years than people in the bone marrow stimulation group (n=30, mean difference=12.4 points, p=0.04). Another subgroup analysis of people who were sport active found that people who had the scaffold procedure (n=16) had greater IKDC improvements than people who had bone marrow stimulation at 2 years (n=11, mean difference 16 points, p=0.03). A clinically meaningful but not statistically significant difference in improvements in IKDC scores was seen between people who had osteochondral dissecans who had the scaffold procedure (n=15) and people who had the bone marrow stimulation procedure (n=12, mean difference 12 points, p=0.14).	
Shive, 2015	**SF-36 (mental and physical subscales)** There were no statistically significant differences between the scaffold and microfracture groups in the change from year 1 to 5 on either the mental (p=0.13) or physical (p=0.48)	**Overall adverse event rates** There were 54 adverse events in 31 people in the 5-year follow up and more than 90% were mild to moderate:

First author, date	Efficacy outcomes	Safety outcomes
	subscales of the SF-36. Both groups maintained the improvements seen at year 1 at year 5. While not statistically significant, the mental subscale dropped below baseline at the 5-year follow up in the microfracture group. **WOMAC** Both the scaffold and microfracture groups had a statistically significant improvement from baseline to 5 years in all 3 WOMAC subscales ($p<0.001$). There were no between group differences in the mean change from year 1 scores, adjusted for baseline, for the pain ($p=0.47$), stiffness ($p=0.24$) or function ($p=0.33$) subscales. **Defect filling** At 5 years, the scaffold group had a statistically significantly greater increase in percent defect fill than the microfracture group ($p=0.02$) after adjusting for lesion volume: • At 5 years, mean percent fill in the scaffold group was 93.8% (SE 1.2) • At 5 years, mean percent fill in the microfracture group was 87.0% (SE 2.9)	• 19% (13 people) in the scaffold group had an adverse event including 2 unexpected and procedure-related adverse events in 1 person, 2 unexpected device-related events in 1 person, and 1 expected and procedure-related adverse event in 1 person. All were mild to moderate and ongoing at 5 years. • 27% (18 people) in the microfracture group had an adverse event including 2 expected procedure-related events that were mild and ongoing at 5 years. **Knee pain** Knee pain was the most common adverse event: • 11% of people in the scaffold group • 17% of people in the microfracture group
Gille, 2021	The number of people with data available at each year's follow up was only reported for Lysholm data. Of 131 people whose data was included in any analysis, 106 had Lysholm data at year 1, 61 at year 2, 44 at year 3, 35 at year 4, 27 at year 5, 22 at year 6 and 9 at year 7.	Safety outcomes were not reported in this study.

First author, date	Efficacy outcomes	Safety outcomes
	KOOS Mean KOOS statistically significantly increased from baseline (mean 45) to 1 year (mean 77, p<0.001). This improvement was maintained every year up to 7 years (p<0.001). **VAS** Median VAS statistically significantly decreased from baseline (median 5.5) to 1 year (median 2.3, p<0.001). The authors report that this was maintained up to 7 years (p<0.001), but there was a slight, but not statistically significant increase, by year 7. **Lysholm score** Mean Lysholm score statistically significantly increased from baseline (mean 46.9) to 1 year (mean 83.8, p<0.001, n=106 people). This improvement was maintained every year up to 7 years (p<0.001, n=9), with no significant difference in score at any follow-up timepoint. **Covariate analyses** Covariate analyses for age, sex, previous surgery, defect location and size were done. There was no statistically significant effect of any of the covariates on any of the outcomes assessed.	

First author, date	Efficacy outcomes	Safety outcomes
de Girolamo, 2019	At 60 months, 10 out of 12 people were followed up in each arm. At 100 months, 7 out of 12 people were followed up in the scaffold-only group and 9 out of 12 people in the scaffold plus bone marrow aspirate concentrate group. **KOOS** This was only assessed at 60 and 100 months. Exact values were not reported for this outcome. There was no statistically significant difference between groups at either timepoint (p not reported). The authors report that KOOS was satisfactory for pain and daily activities subscores up to 100 months. There was a slight progressive decrease in sport and quality of life subscales between 60 and 100 months. **VAS (pain)** At all postoperative timepoints (6, 12, 24, 60 and 100 months), the VAS score was statistically significantly better compared with baseline for both the scaffold and scaffold plus bone marrow aspirate concentrate groups. All timepoints showed highly statistically significant decreases in pain in the scaffold plus bone marrow aspirate concentrate group. The only timepoint with a statistically significant difference between groups was 12 months, favouring the scaffold plus bone marrow aspirate concentrate group (mean difference 1.9, 95% CI 0.5 to 3.3, n=22 people).	**Arthrosynovitis** 1 person in the scaffold-only group had arthrosynovitis. No other adverse event or complications were recorded in this study.

First author, date	Efficacy outcomes	Safety outcomes
	IKDC (objective) This was only assessed at preprocedure, 6, 12 and 24 months. Objective IKDC scores showed a statistically significantly higher proportion of people whose knee was assessed as 'normal' at 24 months ($p<0.05$) in the scaffold plus bone marrow aspirate concentrate group. The scaffold-only group had a statistically significant improvement at 6 months but no further statistically significant improvement was seen at any other timepoint. **Lysholm score** The scaffold plus bone marrow aspirate concentrate group had statistically significant improvements in Lysholm score compared with baseline at all timepoints ($p<0.001$ at 6, 12, 24, 60, 100 months; n=11 at 6 months, n=9 at 100 months). The scaffold-only group only had statistically significant improvements at 24 and 60 months. The gains at 24 ($p<0.001$) and 60 months ($p<0.05$) were lost at the 100-month timepoint. There was a statistically significant difference between groups at 12 months (mean difference 9.9, 95% CI 2.1 to 17.6, $p<0.05$, n=22). **Tegner score** Both groups showed return to pre-injury level of activity from 12 months, with further improvements at 24 months, which then declined at 60 and 100 months. The authors justified this	

First author, date	Efficacy outcomes	Safety outcomes
	as a physiological drop because of the effects of age on sports activity. Scores at last follow up were not significantly lower than pre-injury. **Imaging outcomes including defect filling** Few people in the scaffold-only group contributed MRI data (n=5 and n=2 at 12 and 24 months). At 6 months, more people in the scaffold plus bone marrow aspirate concentrate group had evidence of graft integration but it was comparable at 12 months. The authors report that defect filling was similar between groups at 6, 12 and 24 months.	

Procedure technique

Three of 6 meta-analyses did not mention specific technologies used but 1 did report that a mixture of scaffolds were included (Migliorini 2021a). The meta-analyses that did report what scaffolds were used also reported that multiple technologies were included in their review (Kim 2020a, Tan 2023, da Cunha 2020).

Most often, studies in the meta-analyses used Chondro-Gide (Geistlich Pharma AG) with microfracture. This is a collagen scaffold that is sutured or glued over the microfracture site. This technique with this technology has been trademarked with the term 'Autologous Matrix-Induced Chondrogenesis'. This technique was also used in the registry study (Gille 2021). Other technologies referred to in the meta-analyses were Hyalofast, ChonDux and Chondrotissue (BioTissue AG).

The RCT of 251 people used Agili-C (Cartiheal Ltd), which is an aragonite-based biphasic implant (Altschuler 2023). This is press-fit into a purpose-drilled hole that penetrates the subchondral bone. There was no explicit mention of using microfracture or other bone marrow stimulation procedure in this study.

The RCT by Kim (2020b) used CartiFill (Sewon Cellontech, Seoul, Korea), which is an atelocollagen gel scaffold. This was mixed with thrombin and fibrinogen and applied to the microfractured site. The authors described this as a collagen-augmented chondrogenesis technique.

The RCT by Kon (2018) used MaioRegen (Fin-Ceramica Faenza S.p.A., Italy), which is a bioceramic composite scaffold that is press-fit into a hole drilled into the subchondral bone. There was no explicit mention of using microfracture or other bone marrow stimulation procedure in this study.

In the RCT 5-year follow up (Shive 2015) BST-CarGel (Piramal Life Sciences, Bio-Orthopaedics Division) was used. This is a gel scaffold containing chitosan and was applied after microfracture.

Some studies augmented the procedure with other materials too. The network meta-analysis excluded augmented procedures. Meta-analyses by the same group comparing the procedure with microfracture included studies that immersed the scaffold in bone marrow concentrate before applying it to the lesion (Migliorini 2022a and 2022b). Similarly, many studies in the meta-analyses by Kim (2020), Tan (2023) and da Cunha (2020) included augmentations to the procedure such as the addition of platelet-rich plasma gel, bone marrow aspirate, or bone marrow aspirate concentrate. The RCT of 24 people (de Girolamo 2019) compared microfracture and Chondro-Gide (Geistlich Pharma AG) with microfracture, Chondro-Gide and bone marrow aspirate concentrate.

Some studies included people who had concomitant procedures, such as high tibial osteotomy, meniscal treatments such as partial meniscectomy or concomitant anterior cruciate ligament surgery. The meta-analysis including 29 studies that compared the scaffold procedure with microfracture alone (Kim 2020a) excluded studies that included people who had concomitant high tibial osteotomy.

Efficacy

KOOS

KOOS outcomes were reported in 6 studies. In the meta-analysis including 24 studies that compared open with arthroscopic approaches to the procedure (Tan 2023) both groups had statistically significant improvements from baseline ($p<0.001$). There was no statistically significant difference in KOOS score at the last follow up between the open and the arthroscopic groups (mean difference 8.1, $p=0.19$). The RCT of 251 people comparing the procedure with surgical

standard of care (Altschuler 2023) found statistically significant differences favouring the scaffold group at all timepoints (6, 12, 18 and 24 months). This contrasted with the RCT of 100 people that compared the procedure with microfracture alone (Kim 2020b), which reported no statistically significant difference in improvement between groups at 12 or 24 months. In this study, both groups did have statistically significant improvements compared with baseline overall and on subscales, except for the sport and recreation subscale for the microfracture only group at 12 months (p=0.06). This was similar in the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018). Both the scaffold and bone marrow stimulation only groups had statistically significant improvements from baseline to 2 years postoperatively but no statistically significant difference between groups was found (p value not reported). In the registry study (Gille 2021), mean KOOS statistically significantly increased from baseline (mean 45) to 1 year (mean 77, p<0.001). This improvement was maintained every year up to 7 years (p<0.001), although it is likely that about 9 people contributed data at the 7-year follow up. The RCT of 24 people comparing the procedure with and without bone marrow aspirate concentrate (de Girolamo 2019) also examined this at 60 and 100 months. Exact values were not reported for this outcome but the authors reported no statistically significant differences between groups at either timepoint (p value not reported). The authors report that KOOS was satisfactory for pain and daily activities subscores up to 100 months. There was a slight progressive decline in sport and quality of life subscales.

IKDC (subjective)

Subjective IKDC scores were reported in 7 studies. Meta-analysis level evidence showed consistently better outcomes in the procedure group than comparators. In the meta-analysis including 18 studies that compared the procedure with microfracture alone (Migliorini 2022a), people who had the procedure had a statistically significant greater IKDC score than people who had microfracture

alone (weighted mean difference between groups was 11.8 points, p<0.001). The increase in the procedure group was statistically significant and greater than the MCID of 15 points (mean 34 points, p<0.001). This was similar in the meta-analysis including 29 studies that compared the procedure with microfracture alone (Kim 2020a). After a minimum of 2 years, improvements in IKDC scores were statistically significantly larger in the AMIC group than the microfracture group (p<0.001) and the mean improvement was 45.9 points. Endpoint mean IKDC scores were also higher for people that had the procedure than people who had mACI in the meta-analysis including 47 studies (Migliorini 2022b). When comparing open with arthroscopic approaches to the procedure, the meta-analysis of 24 studies (Tan 2023) found no statistically significant difference between groups (p=0.29). In the meta-analysis of 10 studies (da Cunha 2020), weighted mean improvement in IKDC score was 33.2 points at a median of 24 months (range 12 to 84).

Individual RCT evidence had mixed findings. In the RCT of 251 people comparing the procedure with surgical standard of care (Altschuler 2023), mean change in IKDC scores was greater than the MCID at 6, 12, 18 and 24 months. Also, the difference between the scaffold and surgical standard of care group was statistically significant at all timepoints (p<0.001 reported at 12, 18 and 24 months). But both the RCT of 100 people that compared the procedure with microfracture alone (Kim 2020b) and the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018) found statistically significant improvements in IKDC score compared with baseline up to 2 years but did not find a difference between groups.

VAS (pain)

VAS was reported in 8 studies. Meta-analysis findings were mixed. In the meta-analysis including 18 studies that compared the procedure with microfracture alone (Migliorini 2022a), people who had the procedure had a statistically

significant mean decrease of 3.9 points at an average of 40 months (p<0.001). This was statistically significantly lower than in people who had microfracture alone (weighted MD between groups was -1.0 points, p=0.04). Mean improvement was not statistically significantly lower in the meta-analysis including 29 studies that compared the procedure with microfracture alone (Kim 2020a). The mean improvement was 4.8 points in the procedure group compared with 3.2 points in the microfracture group. In the meta-analysis including 47 studies that compared the procedure with mACI (Migliorini 2022b), there was no statistically significant difference in VAS scores between people who had the procedure and people who had mACI (MD 0.07, p=not significant). In the meta-analysis including 24 studies that compared open with arthroscopic approaches (Tan 2023), both groups had statistically significant improvements from baseline (p<0.001). But there was a statistically significant difference in VAS score at the last follow up, favouring the arthroscopic group over the open surgery group (mean difference 6.6 points out of 100, p=0.007). In the meta-analysis of 10 studies, weighted mean decrease in VAS score was 4.2 points at a median of 24 months (range 12 to 30).

Both the RCT of 100 people that compared the procedure with microfracture alone (Kim 2018) and the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018) found no statistically significant differences between groups up to 2 years. But the RCT by Kim (2018) found there were more people in the scaffold group (43%) than the microfracture only group (33%) with a MCID compared with baseline on the VAS scale at 24 months (OR 2.81, p=0.047). In the registry study (Gille 2021), median VAS statistically significantly decreased from baseline (median 5.5) to 1 year (median 2.3, p<0.001). The authors report that this was maintained up to 7 years (p<0.001), but there was a slight but not statistically significant increase, by year 7. It is likely that about 9 people contributed data at the 7-year follow up in this study. In the RCT of 24 people comparing the procedure with and without bone marrow aspirate

concentrate (de Girolamo 2019), VAS score was statistically significantly better compared with baseline in both groups at 6, 12, 24, 60 and 100 months. While all timepoints showed highly statistically significant decreases in pain in the scaffold plus bone marrow aspirate concentrate group, the only timepoint with a statistically significant difference between groups was 12 months (mean difference 1.9).

Lysholm score

Lysholm score was reported in 6 studies. The meta-analysis including 18 studies that compared the procedure with microfracture alone (Migliorini 2022a) did not report comparative outcomes for Lysholm. But it found that people who had the procedure had a statistically significant mean increase of 28 points at a mean of 40 months (95% CI 26.9 to 29.1, p<0.001). The authors reported the MCID was 10 points. When compared against microfracture in the meta-analysis of 29 studies (Kim 2020), improvements in Lysholm scores were not statistically significantly greater in the procedure group than the microfracture group (p=0.38). In the meta-analysis of 47 studies (Migliorini 2022b), people who had the procedure had a statistically significant higher mean Lysholm score than people who had mACI. The network meta-analysis including 103 people who had the procedure (Migliorini 2021a) found that people who had this procedure had higher Lysholm scores compared with people who had microfracture alone, ACI, mACI or OAT (SMD 4, 95% CI -10 to 18). In the registry study (Gille 2021) mean Lysholm score statistically significantly increased from baseline (mean 46.9) to 1 year (mean 83.8, p<0.001, n=106 people). This improvement was maintained every year up to 7 years (p<0.001, n=9), with no significant difference in score at any follow-up timepoint. It is likely that about 9 people contributed data at the 7-year follow up in this study. In the RCT of 24 people comparing the procedure with and without bone marrow aspirate concentrate (de Girolamo 2019), the scaffold plus bone marrow aspirate concentrate group had statistically significant improvements in Lysholm score compared with baseline at all timepoints up to

100 months (p<0.001). The scaffold-only group only had statistically significant improvements at 24 and 60 months. The gains at 24 (p<0.001) and 60 months (p<0.05) were lost at the 100-month timepoint in this group. There was a statistically significant difference between groups at 12 months only (mean difference 9.9, p<0.05, n=22).

Tegner score

Tegner scores were reported in 6 studies. In the meta-analysis including 18 studies that compared the procedure with microfracture alone (Migliorini 2022a), people who had the procedure had a statistically significant mean increase of 0.8 points (p=0.03) at a mean of 40 months. This was greater than the cited MCID of 0.5 points. The authors did not report comparative outcomes with microfracture in this study. When compared against microfracture in the meta-analysis of 29 studies (Kim 2020a), improvements in Tegner scores were not statistically significantly larger in the procedure group than the microfracture group (p=0.37) at a minimum of 2 years of follow up. Similarly, there was no statistically significant difference in Tegner scores between people who had the procedure and people who had mACI in the meta-analysis of 47 studies (Migliorini 2022b, MD 0.3, p=not significant). In the network meta-analysis including 103 people who had the procedure (Migliorini 2021a), people who had this procedure had the highest Tegner score (SMD -2.1, 95% CI -3.2 to -1.0). In the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018) both the scaffold and bone marrow stimulation only groups had statistically significant improvements from baseline to 2 years postoperatively (p value not reported). Also, there were no statistically significant differences between groups (p value not reported). In the RCT of 24 people comparing the procedure with and without bone marrow aspirate concentrate (de Girolamo 2019), both groups showed return to pre-injury level of activity from 12 months. There were further improvements at 24 months, which then declined at 60 and 100 months. The authors justified this as a physiological drop because of the effects of age on

sports activity. Scores at last follow up were not significantly worse than pre-injury.

WOMAC

One study reported WOMAC scores. In the 5-year follow up of an RCT including 60 people (Shive 2015), both the scaffold and microfracture groups had a statistically significant improvement from baseline to 5 years in all 3 WOMAC subscales ($p<0.001$). There were no between group differences in the mean change from year 1 scores, adjusted for baseline, for the pain ($p=0.47$), stiffness ($p=0.24$) or function ($p=0.33$) subscales.

SF-36

One study reported SF-36 scores. In the 5-year follow up of an RCT including 60 people (Shive 2015), there were no statistically significant differences between the scaffold and microfracture groups in the change from year 1 to 5 on either the mental ($p=0.13$) or physical ($p=0.48$) subscales of the SF-36. While not statistically significant, the mental subscale dropped below baseline at the 5-year follow up in the microfracture group.

MOCART

Four studies reported MOCART outcomes. In the meta-analysis including 29 studies that compared the procedure with microfracture alone (Kim 2020a), after a minimum of 2 years, overall MOCART scores were statistically significantly better in the procedure group than the microfracture group ($p=0.005$). The mean score in the procedure group was 69.3, compared with 41.0 in the microfracture group. In the meta-analysis including 24 studies that compared open with arthroscopic approaches to the procedure (Tan 2023), the open surgery mean was 64.59 (95% CI 57.4 to 71.8) and the arthroscopic mean was 58.3 (95% CI 50.5 to 66.1). In the RCT of 100 people that compared the procedure with microfracture alone (Kim 2020b) total MOCART score at 12 months was not

statistically different between the scaffold group (mean 50.9, SD 19.8) and microfracture group (mean 45.7, SD 19.9, p=0.23). But 3 subscales of MOCART at 12 months favoured the scaffold group: degree of defect repair and filling, integration with the border zone and effusion (p=0.02, p=0.006 and p=0.008, respectively). Similarly, there was no statistically significant difference between groups in the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018).

Defect fill

Defect fill was reported in 5 studies. In the meta-analysis including 29 studies that compared the procedure with microfracture alone at 2 years (Kim 2020a), defect filling rate was statistically significantly better in the procedure group than the microfracture group (77% compared with 48%, OR 1.58, p=0.008). In the meta-analysis of 10 studies (da Cunha 2020), findings varied by scaffold used and when more than one study reported findings for the same technology, the results also tended to vary. Overall, defect filling ranged from 19% to 'complete'. In the RCT of 251 people comparing the procedure with surgical standard of care (Altschuler 2023), 89% of the scaffold group had 75% or more defect fill compared with 31% in the surgical standard of care group at 24 months (p<0.001). Also, a less than 50% defect fill was reported for 1% of the scaffold group compared with 50% of the surgical standard of care group at 24 months. Lower overall fill rates were seen at 12 months in the RCT of 100 people that compared the procedure with microfracture alone (Kim 2020b) but this still favoured the procedure group; 50% or higher defect filling was seen in 42% of the scaffold group and 29% of the microfracture group (OR 4.0, p=0.01). In the 5-year follow up of an RCT including 60 people (Shive 2015), the scaffold group had a statistically significant greater increase in percent defect fill than the microfracture group (p=0.02) after adjusting for lesion volume (94% and 87% fill was seen in the procedure and microfracture groups, respectively). In the RCT of 24 people comparing the procedure with and without bone marrow aspirate

concentrate (de Girolamo 2019), the authors report that defect filling was similar between groups at 6, 12 and 24 months although only 2 people completed follow up in the scaffold-only group.

IKDC objective score

Two studies reported IKDC objective outcomes. In the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018), the percentage of people assessed as having 'normal' or 'nearly normal' knees increased from baseline to 2-years of follow up in the scaffold group. They did not report if this was statistically significant. The scores also increased in the bone marrow stimulation group but the authors reported this was not statistically significant (p value not reported). There was no statistically significant difference between groups (p value not reported). In the RCT of 24 people comparing the procedure with and without bone marrow aspirate concentrate (de Girolamo 2019), IKDC objective score was assessed at baseline, 6, 12 and 24 months. They found a statistically significantly higher proportion of people whose knee was assessed as 'normal' at 24 months ($p<0.05$) in the scaffold plus bone marrow aspirate concentrate group. The scaffold-only group had a statistically significant improvement at 6 months but no further statistically significant difference after this timepoint.

Covariate analyses

Three studies reported covariate analyses (Altschuler 2023, Kon 2018, Gille 2021).

Lesion size was assessed in all 3 studies. In the RCT of 251 people (Altschuler 2023) the difference between treatment groups in KOOS improvement at 24 months showed statistically significant variance by lesion size. People with lesions greater than 3 cm^2 had more improvement than people with smaller lesions (p not reported). There was no effect of lesion size on improvement from

baseline to 2-year follow up on the IKDC subjective in the RCT of 100 people (Kon 2018) or any outcome assessed in the registry study (Gille 2021).

In the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018), an analysis of the scaffold procedure group showed that people with grade 4 lesions and who did not have concomitant anterior cruciate ligament surgery had better IKDC outcomes ($p<0.05$). A subgroup of people with deep lesions involving the subchondral bone who did not have anterior cruciate ligament surgery were analysed for between group differences. From baseline to 2 years, people in this subgroup who had the scaffold procedure (n=27) had more improvement on the IKDC subjective score at 2 years than people in the bone marrow stimulation group (n=30, p=0.04). Another subgroup analysis of people who were sport active found that people who had the scaffold procedure (n=16) had greater IKDC improvements than people who had bone marrow stimulation at 2 years (n=11, p=0.03). A clinically meaningful but not statistically significant difference in improvements in IKDC scores was seen between people who had osteochondral dissecans who had the scaffold procedure (n=15) and people who had the bone marrow stimulation procedure (n=12, p=0.14).

Other covariates were assessed and found to have no effect on outcomes. The RCT of 251 people comparing the procedure with surgical standard of care (Altschuler 2023) found no effect of OA or age. In the RCT of 100 people (Kon 2018) outcomes on the IKDC subjective did not statistically significantly vary by age, sex or lesion size. The registry study (Gille 2021) found age, sex, previous surgery and defect location had no significant effect on any of the outcomes assessed.

Safety

Ten of 11 studies reported on adverse effects of the procedure. When reported, overall adverse event rates are presented in Table 3. Specific events are reported below.

Surgical failure

Failure rate was reported in 6 studies. Not all studies defined how this was measured. Details are reported alongside study findings. The meta-analysis including 18 studies that compared the procedure with microfracture alone with a mean of 40 months of follow up (Migliorini 2022a) reported a failure rate of 4% for people who had the procedure (9 out of 236 people). Failure was not defined in this study. A lower rate of 2% was reported in the meta-analysis including 47 studies that compared the procedure with mACI with a mean of 38 months of follow up (Migliorini 2022b). This was statistically lower than the rate reported in the mACI group, which was 7% (OR 0.2, 95% CI 0.0 to 0.9, p=0.04). Failure was also not defined in this study. In the network meta-analysis including 103 people who had the procedure with a mean of 36 months of follow up (Migliorini 2021a), failure was defined as pain or catching symptoms recurrence, partial or complete displaced delamination at MRI or arthroscopy. The procedure group had the lowest failure rate compared with microfracture, ACI, mACI and OAT (log OR 0.2, 95% CI -2.0 to 1.7). In the meta-analysis including 24 studies that compared open with arthroscopic approaches to the procedure with a mean follow up of 38 months in the procedure group (Tan 2023), 3 open surgery studies reported that treatment failed in 11 people (not defined). The RCT of 251 people comparing the procedure with surgical standard of care (Altschuler 2023) defined surgical failure as any secondary invasive intervention in the treated joint (for example, open, mini-open surgical or arthroscopic procedures, as well as any intraarticular injection), regardless if related or unrelated to the original treatment. There were more treatment failures in the surgical standard of care group (21%) than the

scaffold group (7%) over a 2-year follow up (p=0.002). In the RCT of 100 people that compared the procedure with bone marrow stimulation with 2-year follow up (Kon 2018), failure was defined as the need for reintervention on the same defect based on the persistence or recurrence of symptoms. There were 2 surgical failures in the scaffold group and none in the bone marrow stimulation group (denominator not reported).

Revision surgery rate

Revision surgery rate was reported in 3 studies. In the meta-analysis including 18 studies that compared the procedure with microfracture alone (Migliorini 2022a) the revision rate for people who had the procedure was 5% over a mean of 44 months of follow up. The OR favoured the procedure compared with microfracture, OR 0.16 (95% CI 0.06 to 0.44). In the meta-analysis including 47 studies that compared the procedure with mACI (Migliorini 2022b), there was no statistically significant difference in the revision rate between people who had the procedure and people who had mACI over a mean of 38 months of follow up (OR 0.5, 95% CI 0.2 to 1.0, p=0.07); the revision rate was 7 of 117 observations in the procedure arm and 39 of 328 observations in the mACI arm. The network meta-analysis including 103 people who had the procedure with a mean of 36 months of follow up (Migliorini 2021a) found that people who had the procedure had the lowest revision surgery rate compared with microfracture, ACI, mACI and OAT (log OR 0.9, 95% CI −0.8 to 2.6). Overall revision surgery rate was not reported in the RCT of 251 people comparing the procedure with surgical standard of care with 24 months of follow up (Altschuler 2023). But, they reported that no people in the scaffold group had revision surgery because of OA progression and 5% of people (4 out of 84) in the surgical standard of care group had revision surgery because of OA progression.

Hypertrophy

Rate of hypertrophy was reported in 3 studies. The meta-analysis including 18 studies that compared the scaffold procedure with microfracture alone (Migliorini 2022a) reported that at last follow up (mean 40 months, SD 27 months), no people who had the scaffold procedure had signs of hypertrophy. The meta-analysis including 47 studies that compared the scaffold procedure with mACI (Migliorini 2022b) reported there was no statistically significant difference in the hypertrophy rate between people who had the scaffold procedure and people who had mACI (OR 0.1, p=0.05). Average follow up was 38 months in this study (SD 22). The network meta-analysis including 103 people who had the procedure (Migliorini 2021a) had an average follow up of 36 months (range 24 to 60). Among the included interventions (microfracture, OAT, ACI and mACI), microfracture had the lowest rate of hypertrophy and the scaffold procedure had the second lowest rate of hypertrophy (log OR 0.2, 95% CI -1.4 to 1.8).

Muscle atrophy

In the RCT of 251 people comparing the procedure with surgical standard of care with 24 months of follow up (Altschuler 2023) 1% of people (2 out of 167) in the scaffold group had muscle atrophy that persisted at last follow up.

Arthroplasty

In the meta-analysis including 47 studies that compared the procedure with mACI with a mean of 38 months of follow up (Migliorini 2022b), there was no statistically significant difference in the knee arthroplasty rate between people who had AMIC and people who had mACI (OR 0.5, p=0.4); 2% in the procedure group (2 out of 126) and 3% in the mACI group (2 out of 64). In the meta-analysis including 24 studies that compared open with arthroscopic approaches to the procedure with a mean follow up of 38 months in the procedure group (Tan 2023) 4 studies reported that 5 people had arthroplasty.

Infection and septic arthritis

The meta-analysis including 24 studies that compared open with arthroscopic approaches to the procedure with a mean follow up of 38 months in the procedure group (Tan 2023) noted that 2 arthroscopic and 4 open surgery studies reported whether there were any infections. None of these studies reported infections. The meta-analysis of 10 studies with a range of follow up from 12 to 84 months reported that in 1 study (da Cunha 2020), cellulitis was reported in 1 person. In the RCT of 251 people comparing the procedure with surgical standard of care with 24 months of follow up (Altschuler 2023), 1 person in the scaffold group had septic arthritis. The implant was removed followed by surgical debridement and antibiotics. This study also reported wound complications; 1% (2 out of 167) of people in the scaffold group and 1% (1 out of 84) in the standard of care group had wound complications requiring antibiotics and prolonged dressing.

Arthrosynovitis

In the RCT of 24 people comparing the procedure with and without bone marrow aspirate concentrate with up to 100 months of follow up (de Girolamo 2019), 1 person in the scaffold-only group had arthrosynovitis.

Deep vein thrombosis

Two studies reported whether there were any deep vein thrombosis events. In the meta-analysis including 24 studies that compared open with arthroscopic approaches to the procedure (Tan 2023), 1 arthroscopic study reported that 3 people had deep vein thrombosis and 2 open surgery studies reported that there were no deep vein thrombosis (mean follow up in the procedure group was 38 months in this meta-analysis). In the RCT of 251 people comparing the procedure with surgical standard of care over 24 months of follow up (Altschuler 2023), 1 person in each group had deep vein thrombosis, which was managed pharmacologically.

Haematoma

In the meta-analysis of 10 studies, 1 study reported that 1 person developed haematoma (da Cunha 2020; range of follow up was 12 to 84 months).

Swelling, effusion and other postoperative symptoms

In the RCT of 251 people comparing the procedure with surgical standard of care with 2-year follow up (Altschuler 2023), 5% of people in both groups had swelling and effusion. These were not considered serious adverse events. The RCT of 100 people that compared the procedure with bone marrow stimulation with 2-year follow up (Kon 2018) reported 8 minor early postoperative events in the scaffold group and 3 in the bone marrow stimulation group.

Stiffness and decreased range of motion

Stiffness and decreased range of motion was reported in 3 studies. In the meta-analysis including 24 studies that compared open with arthroscopic approaches to the procedure (Tan 2023), 1 arthroscopic study reported no knee stiffness events and 1 open surgery study reported 1 person had knee stiffness (mean follow up in the procedure group was 38 months). In the meta-analysis of 10 studies (da Cunha 2020) 1 study reported that 45% (9 people) needed mobilisation under anaesthesia for knee stiffness (range of follow up was 12 to 84 months). In the RCT of 251 people comparing the procedure with surgical standard of care with 24 months of follow up (Altschuler 2023), 1% (2 out of 167 people) in the scaffold group had decreased range of motion in the index knee compared with baseline.

Joint adhesion

Joint adhesion was reported in the RCT of 100 people that compared the procedure with bone marrow stimulation (Kon 2018). In this study with a 2-year follow up, there were 2 serious and 1 non-serious joint adhesion events in the scaffold group and none in the bone marrow stimulation group.

Knee pain

Three studies reported knee pain as an adverse event. In the meta-analysis of 10 studies with a range of follow up between 12 and 84 months (da Cunha 2020), 1 study reported that the most common event was knee pain (11%). Another study in this review reported that 1 person had persistent pain and early degenerative changes of the knee joint. In another study in this review, 44% of adverse events were pain and swelling and 50% were joint pain. Two events in this study were likely or definitely device-related and classified as mild. In the RCT of 251 people comparing the procedure with surgical standard of care with 24 months of follow up (Altschuler 2023), transient knee pain was the most common adverse event, seen in 15% of the scaffold group compared with 39% of the surgical standard of care group. In the RCT of 100 people that compared the procedure with bone marrow stimulation with 2-year follow up (Kon 2018), there was 1 serious and 1 non-serious persistent pain event in the scaffold group and none in the bone marrow stimulation group. Similarly in the 5-year follow up of an RCT including 60 people (Shive 2015), knee pain was the most common adverse event, in 11% in the scaffold group and 17% in the microfracture group.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following adverse events that were not categorised as anecdotal or theoretical:

- patch displacement

- displacement of fixation pins.

Six professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- Most of the evidence is from outside of the UK.
- There were several meta-analyses, RCTs and a registry study included in the key evidence that explored differences in outcomes on a range of patient-reported and imaging outcomes, between scaffolds without cultured cell implantation and a range of comparator interventions.
- The key evidence explored outcomes at a range of follow ups (from 6 to 100 months).
- Generally, studies found the procedure to reliably show improvements compared with baseline across outcomes, have superior outcomes to comparator interventions for chondral knee defects on the IKDC subjective score and imaging findings, but there were mixed findings across other outcomes when in comparison with other interventions. The non-comparative registry study (Gille 2021) showed statistically significant improvements in KOOS, VAS and Lysholm scores that were maintained up to 7 years.
- A key claimed benefit of the procedure is articular cartilage repair. Data on defect fill and MOCART scores pertain to this. Findings generally indicated that people who had the scaffold procedure had better outcomes on these measures if measured at 2 or more years. Some studies found no difference between groups. One meta-analysis found outcomes varied

between different scaffolds and variations on the procedure (da Cunha 2020).

- Each of the 5 RCTs and the registry study in the key evidence used different scaffolds and all of the meta-analyses included a mixture of scaffolds. Some techniques augmented scaffolds with other substances. At least 1 study in the key evidence may not have used bone marrow stimulation; both the RCT by Kon (2018) and the RCT by Altschuler (2023) did not report using microfracture, but drilled a hole into the subchondral bone and press-fit the scaffold they used.

- There are many other factors that may have influenced variation in safety and efficacy outcomes: many studies included people who had concomitant surgery, the membrane fixation technique varied, rehabilitation protocols were not always defined or varied between studies, whether people were having primary or rehabilitation surgery was not always clear, location and aetiology of the lesion was often mixed. Also, surgical approaches varied although this difference was explicitly researched by Tan (2023) and concluded there was little advantage of one approach over the other. Similar limitations were acknowledged across the discussions in the included meta-analyses. Some authors acknowledged that while these factors may confound the findings, these factors reflect variations in the population of people who would have this procedure in the real world.

- More men or males than women or females were included in the studies in the overview. Cartilage damage progressing to significant OA may be more common in women. Mean age for most studies was between 27 and 39 but the mean in the RCT by Altschuler (2023) and RCT by Kim (2020b) were both older. Cartilage damage as a result of disease, trauma or sport injuries can occur more commonly in adolescents and young adults.

- The meta-analysis by Migliorini (2022a) included a high proportion of retrospective and non-comparative evidence, and it included some studies that augmented with bone marrow concentrate. Two authors of this review were main authors on 2 papers included in the analysis. Similarly, the meta-analysis by Kim (2020a) acknowledges that much of the evidence is retrospective and single arm. Both of these studies had the same research question but they included different studies to each other. They had different efficacy conclusions on the VAS, but both had positive findings for the procedure on the IKDC subjective score. Some more recent evidence was included in the Migliorini (2022a) study. This study references the Kim (2020a) study but does not acknowledge reasons for differences in their findings. One explanation for the differences in findings is that the microfracture arm in the meta-analysis by Kim (2020a) had longer average follow up than the scaffold arm. Neither study reported conflicts of interest.

- The meta-analysis comparing the procedure with mACI (Migliorini 2022b) acknowledged that there were more people and procedures in the mACI arm that may generate biased results in detection of complications. No conflicts of interest were reported in this study.

- The network meta-analysis by Migliorini (2021a) only included prospective, level 1 and 2 evidence. This was at the expense of only including 106 people in the AMIC group and only being able to aggregate findings on 2 outcomes that relate to activity level. Most studies used the Chondro-Gide scaffold after microfracture. One author is the editor in chief of the journal this was published in. No other competing interests were reported. This study did not include studies that used scaffolds augmented with other substances.

- The meta-analysis by Tan (2023) included both RCT and non-RCT level evidence. The authors noted that there was no direct comparative evidence and much more evidence for the open approach than arthroscopic. No conflicts of interest were reported in this study.

- The meta-analysis by da Cunha (2020) reported some conflicts of interest with a company developing enhanced microfracture techniques.

- The RCT by Altschuler (2023) had some imbalances at baseline: there were more mild to moderate instances of OA in the surgical standard of care group and the scaffold arm had more deep osteochondral defects and larger lesions on average. The range of concomitant procedures was limited in this study to reduce bias. This trial was funded by the company that manufactured the scaffold and several authors had conflicts of interest because of financial involvement in the company.

- The RCT by Kim (2020b) was funded by the company that manufactured the scaffold but no other conflicts were reported.

- The RCT by Kon (2018) did not reach its target sample size and the authors acknowledge this may have affected the ability to show statistically significant differences. The study was partly funded by the company that manufactured the scaffold and several conflicts of interest were reported.

- The 5-year follow up of an RCT by Shive (2015) had 25% loss to follow up. The group of people analysed was sampled from the RCT group and they had comparatively higher BMI and lesion size than the original RCT group, although they entered these as covariates in their analysis. The follow-up study was funded by the company that manufactured the scaffold and some conflicts of interest were reported.

- The registry study (Gille 2021) had significant loss to follow up; of 131 people that were included at baseline, only 9 had Lysholm data at 7 years. This is likely reflective of the number of people with data for other outcomes in this study. No conflicts of interest were reported.

- The RCT by de Girolamo (2019) was included in 3 meta-analyses in the key evidence. It was also included in the key evidence because it compared using a scaffold with and without augmentation with bone marrow aspirate concentrate. This is a useful comparison given that the mixture of the evidence from techniques with and without augmentation, but this was a small RCT and so the conclusions are limited in generalisability. The first author of this study received speaker's honoraria from the company that manufactured the scaffold. No other conflicts of interest were reported.

- Professional experts indicate that this procedure is being used to fill a gap between microfracture, which is suitable for small lesions, and more complex or technical procedures with cultured cells or resurfacing, which is suitable for large lesions.

- Any ongoing trials:

    - A Randomised Controlled Trial of Scaffold InSertion and Microfracture Compared to Microfracture Alone for the Treatment of Chondral or Osteochondral Defects of the Knee: The SISMIC Study; ISRCTN 90992837; n=176; UK; **the chief investigator of this NIHR-funded trial said that it was stopped early because the funding was withdrawn. Final enrolment was 10**.

    - A ProSpective, MulticEnter, Concurrently Controlled Clinical Study of Chondro-Gide® ArticUlar Cartilage CoveR for the

Treatment of Large Chondral Lesions in the KnEe (SECURE); NCT04537013; n=234; international (not UK); **estimated completion date November 2026**.

- A Randomized, Controlled, Comparative, Single-blinded, Multi-center Study Evaluating JointRep® and Microfracture in Repair of Focal Articular Cartilage Lesions on the Femoral Condyle or Trochlea, The JMAC Trial; NCT04840147; n=185; Australia and Canada; **estimated study completion date Dec 2025**.
- A Prospective, Multicenter, Randomized, Parallel Controlled Study Evaluating the Safety and Efficacy of Chondro-Gide® Bilayer Collagen Membrane in Knee Cartilage Defect Repair; RCT, n=140; China; NCT05785949; **estimated study completion February 2027**.
- Randomized Study Comparing Two Methods for the Treatment of Large Chondral and Osteochondral Defects of the Knee: Augmented Microfracture Technique versus 3rd Generation of ACI; n=80; Switzerland; NCT05651997; **estimated study completion June 2032.**

Existing assessments of this procedure

No recent publications were identified.

Related NICE guidance

Interventional procedures

- Focal resurfacing implants to treat articular cartilage damage in the knee (2022) NICE's interventional procedures guidance 734 (Recommendation: special arrangements).

- Mosaicplasty for symptomatic articular cartilage defects of the knee (2018) NICE's interventional procedures guidance 607 (Recommendation: standard arrangements).
- Arthroscopic radiofrequency chondroplasty for discrete chondral defects of the knee (2014) NICE's interventional procedures guidance 439 (Recommendation: standard arrangements).
- Partial replacement of the meniscus of the knee using a biodegradable scaffold (2012) NICE's interventional procedures guidance 430 (Recommendation: special arrangements).

Technology appraisals

- Autologous chondrocyte implantation using chondrosphere for treating symptomatic articular cartilage defects of the knee (2018) NICE's technology appraisal guidance 508.
- Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee (2017) NICE'S technology appraisal guidance 477.

Professional societies

- British Association for Surgery of the Knee
- British Orthopaedic Association
- UK Biological Knee Society
- British Association for Sport and Exercise Medicine

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 2 completed submissions. These

were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

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3. Migliorini F, Eschweiler J, Götze C et al. (2022b) Matrix- induced autologous chondrocyte implantation (mACI) versus autologous matrix-induced chondrogenesis (AMIC) for chondral defects of the knee: a systematic review. British Medical Bulletin 141: 47-59
4. Migliorini F, Eschweiler J, Schenker H et al. (2021a) Surgical management of focal chondral defects of the knee: a Bayesian network meta-analysis. Journal of Orthopaedic Surgery and Research 16: 543
5. Tan CHB, Huang XYO, Tay ZQ et al. (2023) Arthroscopic and open approaches for autologous matrix-induced chondrogenesis repair of the knee have similar results: a meta-analysis. Journal of ISAKOS: In press.
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7. Altschuler N, Zaslav, KR, Matteo B et al. (2023) Aragonite-based scaffold versus microfracture and debridement for the treatment of knee chondral and osteochondral lesions: Results of a multicenter randomized controlled trial. The American Journal of Sports Medicine 51: 957-967

8. Kim MS, Chun CH, Wang JH et al. (2020b) Microfractures versus a porcine-derived collagen-augmented chondrogenesis technique for treating knee cartilage defects: A multicenter randomized controlled trial. Arthroscopy: The Journal of Arthroscopic and Related Surgery 36: 1612-1624

9. Kon E, Filardo G, Brittberg M, et al. (2018) A multilayer biomaterial for osteochondral regeneration shows superiority vs microfractures for the treatment of osteochondral lesions in a multicentre randomized trial at 2 years. Knee Surg Sports Traumatol Arthrosc.26: 2704- 2715

10. Shive MS, Stanish WD, McCormack R et al. (2015) BSTCarGel® treatment maintains cartilage repair superiority over microfracture at 5 years in a multicenter randomized controlled trial. Cartilage 6:62–72

11. Gille J, Reiss E, Freitag M et al. (2021) Autologous matrix-induced chondrogenesis for treatment of focal cartilage defects in the knee: a follow up study. The Orthopaedic Journal of Sports Medicine 9: 2325967120981872

12. de Girolamo L, Schonhuber H, Vigano M, et al. (2019) Autologous matrix-induced chondrogenesis (AMIC) and AMIC enhanced by autologous concentrated bone marrow aspirate (BMAC) allow for stable clinical and functional improvements at up to 9 years follow-up: Results from a randomized controlled study. Journal of Clinical Medicine 8: 392

Methods

NICE identified studies and reviews relevant to scaffold insertion without autologous cell culture from the medical literature. The following databases were

searched between 24 February 2016 to 21 November 2023: MEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with chondral knee defects.
- Intervention or test: scaffold insertion without autologous cell culture.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE ALL (Ovid)	21/11/2023	1946 to November 20, 2023

EMBASE (Ovid)	21/11/2023	1974 to 2023 November 17
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	21/11/2023	Issue 11 of 12, November 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	21/11/2023	Issue 10 of 12, October 2023
International HTA database (INAHTA)	21/11/2023	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 Cartilage, Articular/ 33551
2 cartilage diseases/ 5541
3 (($chondral* or cartilag* or joint*) adj4 (fullthick* or full thick* or full-thick* or trauma* or defect* or diseas* or lesion* or injur* or articul* or degener*)).tw. 72152
4 or/1-3 88334
5 (knee* or patella* or menisc* or genu*).tw. 383204
6 4 and 5 24538
7 knee injuries/ 19761
8 or/6-7 40832
9 "prostheses and implants"/ 49979
10 tissue scaffolds/ 29593
11 9 and 10 359
12 guided tissue regeneration/ 2838
13 ((cartilag*or artific* or synthet* or arthroscop* or chondrocyte* or collagen or aragonite) adj4 (scaffold* or patch* or matri* or structur* or microstruct* or micro-struct* or "micro struct*" or implant* or prosthe* or repair* or regener* or engineer* or micro fract* or micro-fract* or resurfac* or re-surfac*)).tw. 57676
14 (AMIC or autologous matrix* induc* chondrogenesis*).tw. 456
15 (autologous* adj4 cell adj4 implant*).tw. 150
16 or/11-15 60938
17 16 and 5 3970
18 8 and 17 2484
19 (chondrotissue or chondro-tissue).tw. 10
20 (chondro-gide or chondro gide).tw. 44
21 MaioRegen Biojoint* System*.tw. 0
22 (Agili-C* or "Agili C*").tw. 6
23 or/19-22 60
24 18 or 23 2525
25 animals/ not humans/ 5139215

26 24 not 25 1988

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Study design, number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Akmese R, Özbek EA, Kocaoğlu H, et al (2021). Comparison of All Arthroscopic Implantation of Chitosan-Based Liquid Scaffold and Hyaluronan-Based Soft Scaffold in the Treatment of Condylar Osteochondral Lesions in the Knee. J Knee Surg 35: 222-230	Retrospective comparative study n=69 (n=37 hyaluronan-based scaffold; n=32 chitosan-based scaffold) Follow-up 24 months	Statistically significant improvements in patient reported and objective functional and radiological assessments were seen at 3 and 12 months postprocedure ($p<0.05$). No further improvements were seen at 24 months. There were no statistically significant differences between the different scaffold groups showing clinical and radiological equivalence.	Prospective and larger studies with longer follow-up were included in the key evidence.
Andrade R, Nunes J, Hinckel BB et al (2021). Cartilage Restoration of Patellofemoral Lesions: A Systematic Review. Cartilage 13: 57-73.	Systematic review n=47 knees had AMIC (of a total 1314 knees in the review). Mean follow-up (overall) 59 months	Weighted mean improvement in IKDC scores after the procedure was 32.5 points, 39.8 points on the KOOS and 27 points on the Lysholm score. Compared with other procedures evaluated in the review these were larger improvements,	Only 4 small case series were included in the AMIC subgroup review. The focus was patellofemoral articular cartilage defects only.

		but inferior results were seen on the Kujala score. Radiological scoring of cartilage repair showed incomplete filling in 40 to 60% of people and 70 to 100% had irregular surface; 60 to 100% had heterogenous cartilage structure. The authors conclude there is no evidence to show that one procedure is superior to another, but all have significant functional improvement with low failure rates.	
Andriolo L, Reale D, Di Martino A, Boffa A, Zaffagnini S, Filardo G (2021). Cell-free scaffolds in cartilage knee surgery: a systematic review and meta-analysis of clinical evidence. Cartilage 12(3): 277-292.	Systematic review and meta-analysis n=23 studies (n=521 people) 3 or more years of follow-up was the last end-point summarised	This systematic review qualitatively and quantitatively summarised clinical scores at 1, 2 and 3 or more years. The meta-analysis of 16 studies showed improvement in clinical scores at 1,2 and 3 or more years compared with baseline. The authors conclude that in the short and mid-term, cell-free scaffolds provide good results but more evidence is needed to see how it compares with cell-based strategies.	Other systematic review and meta-analyses covering similar evidence were included in the key evidence.
D'Ambrosi R, Giacco F, Ragone V & Ursino N (2018). Arthroscopic treatment of osteochondral knee	Case series n=21	Two of 21 people with osteochondral knee defects had knee replacement surgery at 24 and 65 months	Larger, more recent studies were included in the key evidence.

defects with resorbable biphasic synthetic scaffold: clinical and radiological results and long-term survival analysis. International Orthopaedics 43: 2183-2189.	Follow-up 102 months	after the procedure. Overall, statistically significant improvements in clinical outcomes on the KOOS and HSS were seen at an average of 36 and 101 months compared with before the procedure. At an average of 101 months, mean MOCART score was 46 (SD 5). No correlation was seen between clinical and radiographic outcomes.	
D'Antimo C, Biggi F, Borean A et al (2017). Combining a novel leucocyte-platelet-concentrated membrane and an injectable collagen scaffold in a single-step AMIC procedure to treat chondral lesions of the knee: a preliminary retrospective study. European journal of orthopaedic surgery & traumatology 27: 673-681.	Retrospective case series n=25 Follow-up 12 months	A leucocyte-platelet-concentrated membrane in combination with an injectable collagen scaffold (Cartifill) was used in this study. The authors concluded that given no adverse events were observed and the ikdc and VAS scores improved during follow-up, the combined AMIC procedure with membrane was a promising approach for chondral knee defects.	This was included in the meta-analysis by Tan (2023) and da Cunha (2020) in the key evidence. Larger, prospective studies with longer follow-up and more standard procedures were included in the key evidence.
Arshi A, Fabricant PD, Go DE, Williams RJ, McAllister DR, Jones KJ. (2018). Can Biologic Augmentation Improve Clinical Outcomes Following microfracture for	Systematic review n=18 (n=10 studies used scaffolding as adjuvants to microfracture)	The authors narratively compared outcomes between injectable adjuvants or scaffold adjuvants to microfracture with microfracture alone. They conclude	A more recent systematic review with meta-analysis was included.

Symptomatic cartilage Defects of the Knee? A Systematic Review. Cartilage 9: 146-155.	Follow-up ranged from 2 to 5 years	evidence is mixed within the scaffold subgroup, but tends to report equivalent or superior clinical outcomes with no additional safety concerns.	
Astur DC, Lopes JC, Santos MA et al (2018). Surgical treatment of chondral knee defects using a collagen membrane- autologus matrix-induced chondrogenesis. Rev Bras Ortop 53: 733-739.	Retrospective case series n=7 Follow-up 12 months	Mean MOCART score was 66 points at 12 months. Lysholm, Kujala and VAS scores all indicated significant improvements compared with baseline at 12 months. The authors conclude these were favourable outcomes.	This study was included in the meta-analysis by Migliorini (2022a, 2022b) and Tan (2023) in the key evidence. Larger, prospective studies with longer follow up were included in the key evidence.
Bakowski P, Grzywacz K, Prusinska A, et al (2022). Autologous Matrix-Induced Chondrogenesis (AMIC) for Focal Chondral Lesions of the Knee: A 2-Year Follow-Up of Clinical, Proprioceptive, and Isokinetic Evaluation. Journal of Functional Biomaterials 13: 277.	Retrospective case control study (single centre) n=69 (n=48 people had AMIC; n=21 healthy controls) Follow-up 2 years	Compared with baseline, a statistically significant improvement was seen in Lysholm and IKDC outcome scores and almost all objective functional scores analysed up to the 2-year follow up. Compared with healthy controls, postural strategy was significantly worse at 2 years. The authors conclude that evidence of durable effectiveness was seen in their study.	Larger, prospective studies with longer follow-up were included in the key evidence.
Bardas CA, Zsolt GJ, Apostu D, Dan DO, Tomoaia G, Benea HRC, (2018).	Retrospective case series	This study evaluated IKDC outcomes pre and postoperatively. All techniques	This study was included in the meta-analysis by Tan (2023)

Functional results of different repair techniques for knee articular cartilage lesions. Rev Chem 69:3288–91.	n=106 (n=7 had a scaffold) Follow-up 6 months	(debridement, microfracture, osteochondral autologous transfer mosaicplasty and autologous matrix induced chondrogenesis) showed significant improvements. The largest improvement was in the autologous matrix induced chondrogenesis group.	in the key evidence. Studies with a larger scaffold group and longer follow-up were included in the key evidence.
Bertho P, Pauvert A, Pouderoux T, et al (2018). Treatment of large deep osteochondritis lesions of the knee by autologous matrix-induced chondrogenesis (AMIC): Preliminary results in 13 patients. Orthopaedics & traumatology, surgery & research 104: 695-700.	Prospective case series (single centre) n=13 Median follow-up 24 months	At a median of 2 years, 11 of 13 people with osteochondral lesions had significant improvements on the IKDC and KOOS scores. Of the people who did not have significant improvements, one had a history of multiple surgeries and the other had the largest lesion of the sample. The authors conclude that good outcomes were seen in these osteochondral lesions.	This study was included in the meta-analysis by Tan (2023) and da Cunha (2020) in the key evidence. Larger studies with longer follow-up were included in the key evidence.
Bong GSP & Lee YHD, (2022). Injectable Scaffold with microfracture using the Autologous Matrix-Induced Chondrogenesis (AMIC) Technique: A Prospective Cohort Study. Malaysian Orthopaedic Journal 16: 86-93.	Prospective case series (single centre) n=21 knees (31 defects) Average follow-up 43 months	In this single-centre study of injectable scaffolds, on average, statistically significant increases were seen in the Lysholm and the KOOS score (26 points, 23 points respectively) within 1 year and maintained during follow-up. No complications or	Larger studies with randomised evidence were included in the key evidence.

		reinterventions were required in the duration of follow-up. The authors conclude that safe and effective outcomes were seen in the short to medium term.	
Chen Chou AC & Tjoen Lie DT (2020). Clinical Outcomes of an All-Arthroscopic Technique for Single-Stage Autologous Matrix-Induced Chondrogenesis in the Treatment of Articular Cartilage Lesions of the Knee. Arthroscopy 2:353-359.	Retrospective case series (single centre) n=22 Follow-up 24 months	All procedures were performed arthroscopically in this study. Statistically significant improvements in IKDC scores at 6 and 24 months were seen. The authors conclude that an all-arthroscopic method of doing this procedure shows early clinical improvements for people with osteochondral lesions.	This study was included in the meta-analysis by Tan (2023). Larger, prospective studies with longer follow-ups and more clinical outcomes were included in the key evidence.
Dávila Castrodad IM, Kraeutler MJ, Fasulo SM et al (2022). Improved Outcomes with Arthroscopic Bone Marrow Aspirate Concentrate and Cartilage-Derived Matrix Implantation versus Chondroplasty for the Treatment of Focal Chondral Defects of the Knee Joint: A Retrospective Case Series. Arthroscopy, Sports Medicine, and Rehabilitation 4: e411-e416.	Retrospective comparative study n=39 in the sub-analysis that controlled for differences between bone marrow aspirate with cartilage scaffold and chondroplasty groups (total sample 98) Mean follow-up 24 months in the scaffold group, mean follow-up	The bone marrow aspirate concentrate plus cartilage scaffold groups had superior outcomes (VAS, activity score, KOS ADL and KOS Sport subscores), compared with chondroplasty. There were no statistically significant differences in postoperative injections, subsequent surgeries, or conversion to total knee arthroplasty between groups.	Larger and prospective studies and studies with standardised follow-ups were included in the key evidence.

	41 months in the chondroplasty group		
Enea D, Cecconi S, Calcagno S, Busilacchi A, Manzotti S, Gigante A. (2015). One-step cartilage repair in the knee: collagen-covered microfracture and autologous bone marrow concentrate. A pilot study. Knee 22: 30-35.	Case series n=9 Mean follow-up 29 months.	Consecutive patients had microfracture plus collagen membrane immersed in bone marrow concentrate in this single stage procedure. Significant clinical improvements were seen at last follow up.	This study was included in the meta-analyses by Migliorini (2022a, 2022b). Larger studies with longer follow-up were included in the key evidence.
Fossum V, Hansen AK, Wilsgaard T, et al (2019). Collagen-Covered Autologous Chondrocyte Implantation Versus Autologous Matrix-Induced Chondrogenesis. The Orthopaedic Journal of Sports Medicine, 7: 2325967119868212.	RCT n=41 (n=21 in the ACI-C group and n=20 in the AMIC group) Mean follow-up 2 years	In this RCT comparison of AMIC and collagen covered-ACI, there were no statistically significant differences in patient reported outcomes at 2 years after the procedure (KOOS, Lysholm, VAS). At 2 years, 2 of 20 people in the AMIC group had a total knee replacement compared with none in the ACI-C group. The authors report no significant differences in the procedures but indicate long term outcomes will be important.	This RCT was included in the meta-analyses by Migliorini (2021a) and Tan (2023) in the key evidence.
Gao L, Orth P, Cicchiarini M & Madry H (2019). Autologous Matrix-Induced Chondrogenesis: A Systematic Review of the Clinical Evidence. The American Journal of Sports Medicine 47: 222-231.	Systematic review n=245 people in 12 studies focusing on the knee (n=28 studies in total; other joints were included)	In most studies, people reported less pain (VAS), and mostly reported improved knee functional scores within 2 years of the procedure. The range of Lysholm scores improved within the first 2 years and at 5	More recent systematic reviews that largely cover the evidence in this systematic review were included in the key evidence.

	Follow-ups were summarised including a 5 year or greater timepoint.	years but worsened overall in years 2 to 5. Overall, the MOCART score was similar at the first and second post operative years. Reoperation rate was 5 out of 245 for AMIC in the knee. They conclude it is a safe procedure but indications are unclear with the current evidence.	
Ginesin E, Chari NS, Barnhart J et al (2023). Cartilage Restoration for Isolated Patellar Chondral Defects: An updated systematic review. Orthopaedic journal of sports medicine 11: 23259671231153422	Systematic review n=3 AMIC studies (n=24 studies in total in the review) Follow up not reported	The authors reviewed a series of cartilage restoration techniques. They conclude that advanced microfracture techniques showed promise, but indications (including size of lesion) and variability in techniques need to be elucidated in higher-level studies.	There was no meta-analysis in this study. Systematic review and meta-analyses with more, relevant literature were included in the key evidence.
Glasbrenner J, Peterson W, Raschke MJ et al (2020). Matrix-Augmented Bone Marrow Stimulation With a Polyglycolic Acid Membrane With Hyaluronan vs microfracture in Local Cartilage Defects of the Femoral Condyles: A Multicenter Randomized Controlled Trial. The Orthopaedic Journal of Sports Medicine, 8: 2325967120922938.	Multicentre RCT n=24 (n=12 microfracture only; n=12 microfracture with scaffold) Follow-up 108 weeks	Mean lesion size was 1.2cm^2 in this study. There was no statistically significant difference between groups in the percent of defect filling at 12, 54 and 108 weeks. No statistically significant different was found in patient reported outcomes at any time point (KOOS, IKDC, VAS, SF-36). An infected haematoma (serious adverse event) was treated and the	Larger RCTs with longer follow-up were included in the key evidence.

		person recovered in the microfracture plus scaffold group.	
Gobbi A, Chaurasia S, Karnatzikos G et al (2015). Matrix-Induced Autologous Chondrocyte Implantation versus Multipotent Stem Cells for the Treatment of Large Patellofemoral Chondral Lesions: A Nonrandomized Prospective Trial. Cartilage 6: 82-97.	Prospective non-randomised trial n=37 (n=18 bone marrow aspirate concentrate with scaffold, n=19= Maci). Mean follow-up 60 months	All people in this trial had lesions 4cm^2 or larger. Both groups showed significant improvements in all scores from baseline to last follow-up (IKDC, KOOS, VAS, Tegner). The only score that favoured the bone marrow aspirate concentrate group was IKDC at last follow up. MRI showed complete filling of the defects in 76% of patients in Maci and 81% of patients in the bone marrow aspirate concentrate group. The authors conclude both techniques are effective for lesions at least 4cm^2 for at least 3 years.	Larger prospective and randomised studies were included.
Gobbi A, Scotti C, Karnatzikos G, Mudhigere A, Castro M, Peretti GM (2017). One step surgery with multipotent stem cells and Hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45 years. Knee Surg Sports Traumatol Arthrosc 25:2494–501.	Prospective non-randomised comparison study n=40 (n=20 had a scaffold augmented with bone marrow aspirate concentrate) Follow-up 4 years	All people had a hyaluronan-based scaffold and half had treatment augmented with bone marrow aspirate concentrate in this study. Neither group had microfracture. At 2 years, the augmented treatment group showed superior Tegner and KOOS subscores than control. At final follow-up, all outcomes (KOOS, IKDC, VAS Tegner score and	Larger, randomised studies were included in the key evidence.

		MRI evaluation) had significantly improved. Improvements varied by lesion size and number of lesions.	
Gobbi A, Whyte GP, (2016). One-Stage Cartilage Repair Using a Hyaluronic Acid–Based Scaffold With Activated Bone Marrow–Derived Mesenchymal Stem Cells Compared With microfracture: Five-Year Follow-up. American Journal of Sports Medicine 44: 2846-2854.	Prospective non-randomised comparison study n=50 (hyaluronic acid–based scaffold with activated bone marrow aspirate concentrate compared with microfracture alone) Follow-up 5 years	Both groups had significant improvements at 2 years on the IKDC. Tegner, IKDC objective, and Knee injury and Osteoarthritis Outcome Score (KOOS) assessments demonstrated higher scores in the HA-bone marrow aspirate concentrate treatment group compared with microfracture at 5 years. Lysholm and IKDC subjective scores were similar between treatment groups at 5 years. The authors conclude that more durable effects can be observed with the hyaluronic acid based scaffold than microfracture alone.	Larger prospective case series have been included, with similar follow up.
Gobbi A, Whyte GP (2019). Long-term Clinical Outcomes of One-Stage Cartilage Repair in the Knee With Hyaluronic Acid–Based Scaffold Embedded With Mesenchymal Stem Cells Sourced From Bone Marrow Aspirate Concentrate. The American Journal of	Prospective case series n=23 Mean follow-up 8 years	All clinical outcome scores were significantly improved at last follow-up (IKDC, KOOS, Tegner). The authors conclude that good to excellent long term outcomes can be achieved in full thickness lesions with the hyaluronic acid based scaffold with bone marrow aspirate	Larger and randomised prospective studies are included in the key evidence.

Sports Medicine, 47: 1621-1628.		concentrate. Outcomes may be more successful in younger people.	
Gudas R, Maciulaitis J, Staskunas M et al (2019). Clinical outcome after treatment of single and multiple cartilage defects by autologous matrix-induced chondrogenesis. Journal of Orthopaedic Surgery 27: 1-8.	Retrospective case series (single centre) n=15 Median 5 years	A statistically significant increase in mean IKDC score was seen at follow up and 73% of people reported a return to their previous level of sporting activities.	Larger, prospective studies were included. This study was included in the Migliorini 2022a and 2022b meta-analyses in the key evidence.
Guérin G, Pujol N (2020). Repair of large condylar osteochondral defects of the knee by collagen scaffold. Minimum two-year outcomes. Orthopaedics & Traumatology 106: 475-479.	Retrospective case series (single centre) n=17 Mean follow-up 46 months	At follow-up, incomplete scaffold healing was seen on MOCART (MRI assessment of cartilage healing) in 21% of people. This did not correlate with subjective clinical assessment (KOOS, IKDC) scores. The authors suggest that MOCART is difficult to interpret in the medium term and long-term studies are needed to see if the functional subjective scores are stable over time.	Larger, prospective studies were included in the key evidence.
Hoburg A, Leitsch JM, Diedrichs G, et al (2018). Treatment of osteochondral defects with a combination of bone grafting and AMIC technique. Archives of Orthopaedic and Trauma Surgery 138: 1117-1126.	Case series n=15 Mean follow-up 49 months	Osteochondral defects of the knee were treated with a combined bone-grafting and AMIC procedure in this study. All functional scores (IKDC, KOOS, Lysholm) and pain significantly improved during follow-up. The physical subscale of	This study was included in the meta-analysis by Tan (2023) in the key evidence. Larger studies were included in the key evidence.

		the sf-36 showed improvement and the mental health subscale remained stable. Imaging showed mean MOCART was 77 at final follow-up; 21% of lesions had incomplete integration and 36% had incomplete filling.	
Jaramillo Quiceno GA, Sarmiento Riveros PA, Ochoa Perea GA, et al (2023). Satisfactory clinical outcomes with autologous matrix-induced chondrogenesis in the treatment of grade IV chondral injuries of the knee. Journal of ISAKOS 8: 86-93.	Retrospective case series n=50 Follow-up 32 months	Average patient-reported level of satisfaction after the procedure was 8 out of 10 (SD 1.5). The overall score and symptoms and sports activities subscales of the IKDC score statistically significantly improved from baseline at 12, 24 and 32 months. Function and activity of daily living was not statistically significantly improved at 12 months, but was at 24 and 32 months.	Larger, prospective studies with more clinical outcomes were included in the key evidence.
Kaiser N, Jakob RP, Pagenstert G, et al (2021). Stable clinical long term results after AMIC in the aligned knee. Archives of Orthopaedic and Trauma Surgery 141: 1845- 1854.	Retrospective case series n=33 Mean follow-up 9.3 years	Compared with baseline, there was statistically significant improvement in VAS and Lysholm scores at 2 years, which were maintained at last follow-up (mean 9 years). This was consistent across subgroups of lesions in different sites. Two of 33 people had total knee prosthesis. The authors conclude that	This study was included in the Tan (2023) meta-analysis in the key evidence.

		durable results were seen.	
Karpinski K, Häner M, Bierke S, Peterson W, (2021). Matrix-induced chondrogenesis is a valid and safe cartilage repair option for small- to medium-sized cartilage defects of the knee: a systematic review. Knee Surgery, Sports Traumatology, Arthroscopy 29:4213-4222.	Systematic review of RCTs n=136 (n=5 publications about 4 RCTs) Up to 5 years	RCTs showed good comparative effectiveness and safety with other treatment options for small to medium-sized cartilage defects in the knee. The authors conclude the procedure is a good alternative to offer.	Larger, more recent systematic reviews with meta-analyses were included in the key evidence. Three of 4 RCTs in this review were included in other meta-analyses in Table 2.
Kim MS, Koh IJ, Choi YJ, Pak KH, In Y. (2017). Collagen augmentation improves the quality of cartilage repair after microfracture in patients undergoing high tibial osteotomy: A randomized controlled trial. Am J Sports Med 45: 1845-1855.	RCT n=28 (n=14 microfracture only, n=14 microfracture plus scaffold). Follow-up 1 year	All people in this study were also having high tibial osteotomy. Statistically significant clinical improvements (VAS, KOOS, IKDC, Tegner) were seen in both groups, and there were no between group differences (p> 0.1). The scaffold group had superior imaging outcomes compared with microfracture alone. The authors report longer follow up is needed to see if the difference in tissue repair affects clinical outcomes in the longer term.	Larger RCTs with longer follow-up were included.
Kim SJ, Shetty AA, Kurian NM, et al (2020). Articular cartilage repair using autologous collagen-induced chondrogenesis	Prospective case series (single centre) n=30	An atelocollagen (gel) scaffold was injected after microfracture. Statistically and clinically significant improvement was seen in 2 years and	Larger studies with comparative data were included in the key evidence.

(ACIC): a pragmatic and cost-effective enhancement of a traditional technique. Knee Surgery, Sports Traumatology, Arthroscopy 28: 2598-2603.	Follow-up up to 6 years	sustained at 6 years, on Lysholm, KOOS and IKDC scores. Average MOCART score was 79 (SD 10). The authors conclude this can be used for moderate to severe chondral lesions.	
Kon E, Di Matteo B, Verdonk P, et al (2021). Aragonite-based scaffold for the treatment of joint surface lesions in mild to moderate osteoarthritic knees: results of a 2-year multicenter prospective study. Am J Sports Med, 49: 588-598.	Prospective case series n=86 Follow-up24 months	All clinical outcome scores improved significantly from baseline, at 12 and 24 months (KOOS, IKDC). The MRI imaging showed increasing defect filling over time. Revision surgery was needed in 9% of people. The authors conclude using the aragonite scaffold in mild to moderate lesions in OA knees was promising.	Randomised evidence with larger sample of this procedure is included in the key evidence.
Krych AJ, Nawabi DH, Farshad-Amacker NA, et al (2015). Bone Marrow Concentrate Improves Early Cartilage Phase Maturation of a Scaffold Plug in the Knee.	Single centre comparative cohort n=46 (n=11 in the scaffold only arm) Follow-up 12 months	Compared with a cell-free scaffold with no supplement, those supplemented with platelet rich plasma or bone marrow aspirate concentrate had statistically superior cartilage fill at 12 months. There was no statistically significant difference in quantitative assessment that graded cartilage morphology between the platelet rich plasma and scaffold only group, but the bone marrow aspirate	Larger prospective studies with patient reported outcomes and longer follow-up were included in the key evidence.

		concentrate group had statistically superior scores at 12 months.	
Lahner M, Ull C, Hagen M et al (2018). Cartilage Surgery in Overweight Patients: Clinical and MRI Results after the Autologous Matrix-Induced Chondrogenesis Procedure. BioMed Research International 2018: 6363245.	Prospective case series (single centre) n=9 Mean follow-up 15 months	This study focused on outcomes for the procedure in people with overweight. VAS and Lysholm scores both statistically significantly improved after the procedure. Two lesions had to be reoperated on because of persisting knee pain. The authors indicated that success rate is reduced in this procedure when used in people with high BMI.	This stidy was included in the meta-analyses by Migliorini (2022a, 2022b) and Kim (2023). Larger studies with longer follow-ups in less specific patient groups were included in the key evidence.
di Martino A, Kon E, Perdisa F et al (2015). Surgical treatment of early knee osteoarthritis with a cell-free osteochondral scaffold: results at 24 months of follow-up. Injury 46: s33-38.	Prospective case series n=23 Follow-up 24 months	Statistically significant improvements were seen at 12 months and maintained at 24 months on IKDC, and Tegner scores. Activity level was significantly lower than pre-injury. The authors conclude it is a promising option for early osteoarthritic lesions which have failed conservative management, especially for younger people.	Larger studies with longer follow-up were included in the key evidence.
McDermott I (2019). Patellar chondral defect treatment with a cell-free polyglycolic acid–hyaluronan-based implant and platelet-rich fibrin glue after previously failed	Case study n=1 Follow up 9 months	A person with patellofemoral full-thickness defect had previously failed multiple surgeries including microfracture. After microfracture with	Larger studies were included in the key evidence.

microfracture. SAGE Open Medical Case Reports 7: 1-4.		biocompatible resorbable polyglycolic acid–hyaluronan scaffold implant, MRI showed complete cartilage filling at 6 months. This was confirmed with arthroscopy at 9 months.	
Methot S, Changoor A, Tran-Khanh N, Hoemann CD, Stanish WD, Restrepo A, Shive MS, Buschmann MD (2016). Osteochondral biopsy analysis demonstrates that BST-CarGel treatment improves structural and cellular characteristics of cartilage repair tissue compared with microfracture. Cartilage 7:16–28.	Secondary analysis of additional RCT data n=38 (n=21 scaffold group; n=17 microfracture only) Average follow-up 13 months	This study analysed additional data from an RCT published in 2013. The focus was histological assessment of the repair tissue. The authors conclude that use of the scaffold alongside microfracture resulted in better repair tissue (structural and cellular characteristics).	Studies with patient reported outcomes at longer follow-up points were included in the key evidence.
Migliorini F, Eschweiler J, Maffulli N, et al (2021b). Autologous Matrix-Induced Chondrogenesis (AMIC) and microfractures for Focal Chondral Defects of the Knee: A Medium-Term Comparative Study. Life 11: 183.	Non-randomised comparative study (single institution) n=91 Mean follow-up 42 months	On average, people who had AMIC had a statistically significant greater IKDC, Lysholm, Tegner and VAS score at follow-up, and a lower rate of failure and revision surgery. There was no statistically significant difference in the magnetic resonance observation of cartilage repair tissue score, or the rate of arthroplasty. No delamination or hypertrophy were detected.	Larger, prospective studies were included in the key evidence. This study was also included in the meta-analysis by Migliorini et al (2022b) in the key evidence.
Migliorini F, Eschweiler J, Maffulli N, et al	Non-randomised comparative	This sub-study of Migliorini et al (2021a)	This is a likely a sub-group of

(2021c). Management of Patellar Chondral Defects with Autologous Matrix Induced Chondrogenesis (AMIC) Compared to microfractures: A Four Years Follow-Up Clinical Trial. Life 11: 141.	study (single institution) n=38 (n=28 AMIC, n=11 microfracture) Mean follow-up 45 months	focused on outcomes in patellar facet joints. At the last follow-up, people who had AMIC had a statistically significant greater IKDC, Tegner and Lysholm score, and lower VAS than people who had microfracture alone. No statistically significant difference was found in the radiographic findings, or rates of complication (revision, arthroplasty, delamination, hypertrophy). Failure rate was lower in people who had AMIC.	the sample reported in Migliorini et al (2021a). This study was also included in the meta-analysis by Migliorini et al (2022b) in the key evidence.
Mitrousias V, Chalatsis G, Mylonas T et al (2023). Satisfactory patient-reported outcomes in patients treated with impaction bone grafting and autologous matrix-induced chondrogenesis for osteochondral knee defects. Knee surgery, sports traumatology, arthroscopy 31: 5698-5706.	Retrospective case series n=25 Mean follow-up 3.8 years	AMIC was combined with impaction bone grafting in this procedure. At follow-up, quality of life (EQ-5D) all functional scores (IKDC, KOOS, Lysholm) had significantly improved with all patient reported outcomes at least a minimally clinically important difference, except for the sports subscale of KOS. Mean Tegner scores reached pre-injury scores and the patient-assessed acceptable symptom state was 100% positive. Mean MOCART was 53.	Larger, prospective studies of more standard procedures were included in the key evidence.

Miyahira MKC, Novaretti JV, Astur DC, et al (2020). Larger Chondral Lesions Treated with Collagen Membrane – Matrix-Induced Autologous Chondrogenesis – Show Larger Increase in Clinical Scores. Rev Bras Ortop 56: 333-339.	Single-centre case series n=15 Follow-up 12 months	There was statistically significant improvement in Lysholm and IKDC scores after 12 months. Average MOCART score was 65 points. The greatest benefit was observed in larger lesions.	This study was included in the meta-analyses by Miyahara (2022a) and Kim 2023). Larger, prospective studies with longer follow-up were included in the key evidence.
Perdisa F, Filardo G, Sessa A et al (2017). One-Step Treatment for Patellar Cartilage Defects With a Cell-Free Osteochondral Scaffold: A Prospective Clinical and MRI Evaluation. Am J Sports Med 45: 1581-1588.	Prospective case series (single centre) n=34 Follow-up 24 months	This study focused on patellar cartilage lesions. Post-operative scores on the IKDC and Tegner outcomes were statistically significantly improved compared with baseline at 12 and 24 months. MOCART assessment found that 87% of lesions showed complete cartilage filling at 24 months; 96% showed complete integration of the scaffold and 70% showed intact repair tissue surface at final follow-up.	Larger studies with more patient reported outcomes and longer follow-up were included in the key evidence.
Pipino G, Risitano S, Alviano F, Wu EJ, Bonsi L, Vaccarisi DC, Indelli PF (2019) microfractures and hydrogel scaffolds in the treatment of osteochondral knee defects: a clinical and histological evaluation. J Clin Orthop Trauma 10:67–75.	Non-randomised comparative study n=69 (n=46 had microfracture plus injectable hydrogel scaffold; n=23 had microfracture alone).	Microfracture plus hydrogel was assessed at 6, 12 and 24 months and compared with matched control group who had microfractures alone. Significant short-term improvements in pain, stiffness and function were seen when compared with	Randomised studies and studies with longer follow-up were included in the key evidence.

	Follow-up 24 months	patients having microfractures alone.	
Roessler PP, Pfister B, Gesslein M, et al (2015). Short-term follow up after implantation of a cell-free collagen type I matrix for the treatment of large cartilage defects of the knee. International Orthopaedics (SICOT) 39: 2473-2479.	Prospective case series (single centre) n=28 Follow-up 24 months	Within 6 weeks, there was a statistically significant reduction in VAS (pain) compared with preprocedure. Significant improvements in all other outcomes (IKDC, Tegner, KOOS) except the symptoms subscale of the KOOS were seen at 12 months and maintained at 24 months. At 24 months, radiographic imaging showed that 24 of 28 people had complete defect filling.	Larger, comparative studies with longer follow-up were included in the key evidence.
Rosa F, Fernander JC, Delisle J et al (2022). Clinical and quality-of-life outcomes of a combined synthetic scaffold and autogenous tissue graft procedure for articular cartilage repair in the knee. Journal of orthopaedic surgery and research 17: 112.	Case series n=60 people Follow-up 24 months	In this single step procedure, autologous cartilage was grafted into the lesion site with a synthetic scaffold after microfracture. Significant improvements in IKDC, quality of life (physical and mental domains), and VAS were seen.	Larger, comparative studies with longer follow-up were included in the key evidence.
Sadlik B, Puszkarz M, Kosmalska L & Wiewiorski M (2017). All-Arthroscopic Autologous Matrix-Induced Chondrogenesis-Aided Repair of a Patellar Cartilage Defect Using Dry Arthroscopy and a Retraction System. J	Case series (single centre) n=12 Mean follow-up 38 months	This study described arthroscopic method of doing the AMIC procedure. A statistically significant increase in mean KOOS and IKDC scores and decreased in VAS scores was seen postprocedure. Mean MOCART at follow-up was 58.3	This study was included in the study by Lim (2020a) and Tan (2023). Larger, prospective studies with longer follow-up were included in the key evidence.

Knee Surg 30: 925-929.		points. The authors state that the arthroscopic method of doing the procedure is promising but requires confirmation with comparative evidence.	
Schagemann J, Behrens P, Paech A, et al (2018). Mid-term outcome of arthroscopic AMIC for the treatment of articular cartilage defects in the knee joint is equivalent to mini-open procedures. Archives of orthopaedic and trauma surgery 138: 819- 825.	Retrospective case series n=50 Follow-up 2 years	This study compared outcomes between people who had arthroscopic and open surgery for the AMIC procedure. The findings show statistically significant improvement in VAS, KOOS and Lysholm scores 2 years after surgery compared with baseline. There were no statistically significant differences in outcomes between the surgical approaches.	This study was included in the meta-analyses by Kim (2020a), Tan (2023) and Migliorini (2022a, 2022b). Larger, prospective studies with longer follow-up were included in the key evidence.
Schiavone Panni A, Del Regno C, Mazzitelli G et al (2018). Good clinical results with autologous matrix-induced chondrogenesis (Amic) technique in large knee chondral defects. Knee surgery, sports traumatology, arthroscopy 26: 1130-1136.	Retrospective case series n=21 Median follow-up 7 years	A statistically significant improvement in IKDC and Lysholm scores was seen at last follow up. 76% of people rated they were satisfied or extremely satisfied with their outcomes. 67% showed good quality tissue on MRI imaging. The authors conclude that AMIC is effective for full thickness defects greater than 2cm^2.	This study was included in the meta-analysis by Kim (2020a), Tan (2023), da Cunha (2020) and Migliorini (2022a, 2022b). Larger, prospective studies were included in the key evidence.
Schneider U. (2016). Controlled, randomized multicenter study to	RCT	6 of 10 people in the microfracture group refused the allocated	Higher quality RCTs with longer follow

compare compatibility and safety of ChondroFiller liquid (cell free 2-component collagen gel) with microfracturing of patients with focal cartilage defects of the knee joint. J Ortop Surg 1: 1-8.	n=23 (n=13 scaffold, n=10 microfracture) Follow-up 1 year	treatment so were not analysed. Statistically significant improvements in IKDC were seen by month 3 and 6 and maintained at 1 year. The authors report good filling of the lesion.	up and more people were included.
Schüttler KF, Götschenberg A, Klasan A et al (2019). Cell-free cartilage repair in large defects of the knee: increased failure rate 5 years after implantation of a collagen type I scaffold. Archives of Orthopaedic and Trauma Surgery 139: 99-106.	Prospective case series n=28 Follow up 5 years	Good to excellent clinical results were seen in 82% of people, according to KOOSM, IKDC, VAS and Tegner outcomes. Revision surgery was needed in 18%. Repair tissue showed cartilage-like appearance but medium tissue quality, which reduced in MOCART score between 2 and 5 years.	Larger studies were included in the key evidence.
Sciaretta FV, Ascani C, Sodano L et al (2023). One-stage cartilage repair using the autologous matrix-induced chondrogenesis combined with simultaneous use of autologous adipose tissue graft and adipose tissue mesenchymal cells technique: clinical results and magnetic resonance imaging evaluation at five-year follow-up. International Orthopaedics 48@ 267-277.	Prospective case series n=18 Follow-up 60 months	AMIC was combined with autologous adipose tissue graft and adipose mesenchymal cells in this procedure. In grade 3 to 4 lesions, statistically significant increases were seen in IKDC, Lysholm score between baseline and 2 years, which was maintained at last follow up. The authors conclude these outcomes are superior to those seen in AMIC alone.	Larger, comparative studies with more standard procedures were included in the key evidence.

Sessa A, Andriolo L, Di Martino A, et al. (2019). Cell-free osteochondral scaffold for the treatment of focal articular cartilage defects in early knee OA: 5 years' follow-up results. J Clin Med 14: e1978.	Prospective case series n=22 Follow-up 60 months	All outcomes (IKDC subjective and objective, Tegner) improved at 2 years compared with baseline and remained stable at final follow-up. There were no major adverse events. Minor adverse events included joint stiffness. There was a 16.6% failure rate.	Larger prospective studies with similar follow-up were included in the key evidence.
Shaikh N, Seak MKT, & Khan WS (2017). Systematic review on the use of autologous matrix-induced chondrogenesis for the repair of articular cartilage defects in patients. World J Orthop 8: 588-601.	Systematic review n=16 studies Mean follow-up 30 months	The authors conclude that despite improvements on patient reported outcomes in the short term, they required more evidence to understand the long-term effects. They also noted that conclusions could not be drawn about whether the size of the defect, the location and other patient factors affected the outcome.	More recent systematic reviews with meta-analyses were included in the key evidence.
Shanmugaraj A, Coughlin RP, Kuper GN et al (2019). Changing trends in the use of cartilage restoration techniques for the patellofemoral joint: a systematic review. Knee Surgery, Sports Traumatology, Arthroscopy 27: 854-867.	Systematic review n=71 people in 6 studies (n=28 studies in the review in total) Follow up was between 24 and 38 months in 4 studies and not reported in 2.	This systematic review included studies focused on the patellofemoral joint. Three of 4 studies that reported VAS outcomes showed statistically significant improvements, 2 of 2 studies reporting IKDC outcomes showed a statistically significant improvement and 2 of 3 studies reporting	More recent systematic reviews with meta-analyses and less restrictive populations were included in the key evidence.

		KOOS outcomes showed a significant improvement.	
Shetty AA, Kim SJ, Shetty V, et al (2016). Autologous collagen induced chondrogenesis (ACIC: Shetty–Kim technique) – A matrix based acellular single stage arthroscopic cartilage repair technique. Journal of Clinical Orthopaedics and Trauma 7: 164-169.	Case series (single centre) n=30 Follow-up 4 years	A gel scaffold was applied to defects in this study. At 4 years, the Lysholm score, KOOS and IKDC had significantly improved. Average MOCART score was 72.	Larger studies with more methodological detail on data collection and analysis were included in the key evidence.
Shivji FS, Mumith A, Yasen S et al (2020). Treatment of focal chondral lesions in the knee using a synthetic scaffold plug: Long-term clinical and radiological results. Journal of Orthopaedics 20: 12-16	Retrospective case series (single centre) n=11 Mean follow-up for n=6 people 121 months	This study did not recommend using the TruFit plug in full-thickness lesions because of high conversion rate to arthroplasty and failure of plug incorporation and limited evidence of chondral surface regeneration. There was no statistically significant improvement in Oxford Knee Score, Tegner or Lysholm scores or radiological findings.	Larger, prospective studies with more complete follow-up data were included in the key evidence. This device is no longer in use in the UK.
Snow M, Middleton L, Mehta S, et al (2023). A Randomized Trial of Autologous Chondrocyte Implantation Versus Alternative Forms of Surgical Cartilage Management in Patients With a Failed Primary Treatment for Chondral or	RCT n=390 (ACI compared with alternative management, which included n=50 AMIC) Follow-up 1 year	This RCT compared autologous cell implants with alternative cartilage management, including AMIC. A subgroup analysis of the 'alternative management' group found that patient reported functioning on the Lysholm knee	Only a small subgroup analysis of data on the AMIC group was reported in this RCT.

Osteochondral Defects in the Knee. The American Journal of Sports Medicine: 1-12.		scoring scale was not significantly different from matrix-induced-ACI; mean difference=1.7 (95%CI -5.5 to 9).	
Sofu H, Camurcu Y, Ucpunar H, Ozcan S, Yurten H, Sahin V. (2019). Clinical and radiographic outcomes of chitosan-glycerol phosphate/blood implant are similar with hyaluronic acid-based cell-free scaffold in the treatment of focal osteochondral lesions of the knee joint. Knee Surg Sports Traumatol Arthrosc.27: 773-781.	Comparative case series n=46 (n=25 people had microfracture with chitosan-glycerol phosphate/blood implant; n=21 has microfracture plus hyaluronic acid-based scaffold). Mean follow-up 24 months	There were no significant differences between groups at any time interval during the follow-up. Only for those with small lesions was the chitosan-glycerol phosphate/blood group superior to larger lesions in the same group. The authors conclude the hyaluronic acid scaffold group was less sensitive to lesion size, but for small lesions there are some benefits for the comparator procedure.	This study was included in the meta-analysis by da Cunha (2020). Larger studies with longer follow-up were included.
Sofu H, Kockara N, Oner A, Camurcu Y, Issın A & Sahin V (2017). Results of Hyaluronic Acid-Based Cell-Free Scaffold Application in Combination with microfracture for the Treatment of Osteochondral Lesions of the Knee: 2-Year Comparative Study. Arthroscopy 33: 209-216.	Comparative case series n=43 (n=19 hyaluronic scaffold plus microfracture, n=23 microfracture alone) Mean follow-up 26 months	At 12 and 24 months postprocedure, the microfracture plus scaffold groups has statistically significant improvements compared with microfracture alone on the VAS and Lysholm scores. They also had better activity level (Tegner score) at 24 months and faster return to non-impact sports. Complete repair of cartilage was 37% compared with 17%. The authors conclude with uncertainty about	Larger prospective studies with longer follow up were included.

		the clinical significance of these differences.	
Šprláková-Puková A, Štouračová A, Repko et al (2021). Prospective Multiparametric Magnetic Resonance Monitoring of Changes in Lesions of Hyaline Cartilage of the Knee Joint After Treatment by microfractures and Implantation of Biological Collagen Type I Matrix Implants. Academic Radiology 28: 1133-1141.	Prospective comparative study n=25 (n=14 scaffold insertion; n=11 microfracture alone) Follow-up 18 months	This study used imaging techniques to compare AMIC and microfracture outcomes. No statistically significant differences were seen in glycosaminoglycans chains at 6, 12, 18 months. The greatest decrease in this indicator of cartilage changes was in the AMIC group at 12 months. The authors conclude that there was no difference in MRI-detectable outcomes between groups but it may take longer than was observed in this study to see a difference.	Larger, prospective studies with longer follow-up and patient reported outcomes were included.
Steinwachs M, Cavalcanti N, Reddy SMV et al (2019). Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort study of consecutive patients. The Knee 26: 174-184.	Retrospective case series (single centre) n=91 Mean follow up 6 months	This study assessed outcomes in people who had microfracture followed by a liquid bioscaffold in patellar lesions. No reinterventions were seen. Statistically significant decreases in pain, swelling and increases in radiological healing of the cartilage were seen at follow up. No statistically significant changes were seen for range of motion.	This study was included in the Migliorini et al 2022b meta-analysis. Prospective and comparative studies were included.
Steinwachs MR, Gille J, Volz M, et al (2021). Systematic Review and	Systematic review and meta-analysis	Meta-analysis showed clinically significant improvement in pain	Larger and more recent systematic

Meta-Analysis of the Clinical Evidence on the Use of Autologous Matrix-Induced Chondrogenesis in the Knee. Cartilage 13: 42-56.	n=375 (n=12 studies) 137 people had greater than 4 years of follow-up data; minimum of 1 year follow-up was required for inclusion.	on the VAS from baseline to follow-up at 1 to 2 years after the procedure. This remained significant after 3 years. Lysholm and IKDC scores were also significantly improved after 1 and maintained at 3 years.	reviews were included.
Tradati D, de Luca P, Maione A et al (2020). AMIC—Autologous Matrix-Induced Chondrogenesis Technique in Patellar Cartilage Defects Treatment: A Retrospective Study with a Mid-Term Follow-Up. Journal of Clinical Medicine 9:1184.	Retrospective case series n=14 Mean follow-up 69 months	In people with patellofemoral lesions at 12 months, Kujala, IKDC, and VAS scores significantly increased compared with pre-procedure. This effect was maintained at final follow-up. Patient satisfaction was good or excellent in 100% of people.	Larger, prospective studies were included. This study was included in the meta-analysis by Migliorini (2022a) and Tan (2023)
Volz M, Schaumburger J, Frick H et al (2017). A randomized controlled trial demonstrating sustained benefit of Autologous Matrix-Induced Chondrogenesis over microfracture at five years. International Orthopaedics (SICOT) 41: 797-804.	Multicentre RCT n=47 (n=13 microfracture only, n=17 autologous matrix induced chondrogenesis (glued), n=17 autologous matrix induced chondrogenesis sutured) Follow-up 5 years	Whilet the microfracture only group saw an improvement in functional outcomes (modifified Cincinnati score, modified ICRS score, VAS) over the first 2 years, there was a subsequent decline up to 5 years, the autologous matrix induced chondrogenesis groups improved and sustained improvements up to 5 years. MRI examination of defect filling showed superiority in the autologous matrix induced	This RCT was included in the meta-analyses by Migliorini (2021a, 2022a, 2022b), Kim (2020a) and Tan (2023) that was included in the key evidence.

		chondrogenesis groups. No serious adverse events related to the procedure were recorded.	
Waltenspül M, Suter C, Ackermann J et al (2021). Autologous Matrix-Induced Chondrogenesis (AMIC) for Isolated Retropatellar Cartilage Lesions: Outcome after a Follow-Up of Minimum 2 Years. Cartilage 13:1280-1290.	Retrospective case series (single centre) n=31 Mean 4.1 years	The procedure failed in 13% of people at an average of 21 months. 77% of people reported a satisfactory result but only 35% returned to their previous level of sport. Almost all procedures were performed at the same time as corrective surgery for instability.	This was included in the meta-analysis by Migliorini (2022a) in the key evidence. Larger, prospective studies with longer follow ups were included.
Wang D, Nawabi DH, Krych AJ et al (2021). Synthetic Biphasic Scaffolds versus microfracture for Articular Cartilage Defects of the Knee: A Retrospective Comparative Study. Cartilage 13: 1002S-1013S.	Retrospective case series n=132 (n=66 scaffold, n=66 microfracture only) Follow-up 5 years	Both groups had clinically significant improvements in clinical outcomes over 5 years. There were no significant differences between groups at 5 years on the KOS-acitivities of daily living and IKDC scores. Marx activity level scores declined in the microfracture only group but significant improvements were seen in the scaffold group. MRI appearance was superior in the longer term for the scaffold group.	Prospective studies and randomised studies were included.
Wolf MT, Zhang H, Sharma B, Marcus NA, Pietzner U, Fickert S, et al. (2018). Two year follow-up and	Single arm trial n=18	A hydrogel scaffold in combination with microfracture was used in people with full-thickness lesions.	This study was included in the meta-analysis by da Cunha (2020) in the

remodeling kinetics of ChonDux hydrogel for full thickness cartilage defect repair in the knee. Cartilage.11: 447-457.	Follow-up 24 months	Durable tissue restoration over 24 months was seen, with final percent fill of 94% (SD 16%). VAS pain scores reduced between 1 and 6 weeks and IKDC scores significantly improved by approximately 30 points over 24 months. The authors conclude this is a safe adjunct to microfracture.	key evidence. Larger studies with longer follow up were included.
Wylie JD, Hartley MK, Kapron AL et al (2016). Failures and reoperations after matrix assisted cartilage repair of the knee: A systematic review. The Journal of Arthroscopic and Related Research 32: 386-392.	Systematic review n=6 AMIC studies with 163 people (n=66 in total) Follow-up reported at a minimum of 5 years.	Among the evidence aggregated from 163 people, there were 15 reoperations (9%) that included 4 treatment failures (2%), 9 manipulations under anaesthesia (6%), and 2 debridements for graft hypertrophy (1%).	More recent systematic reviews and long-term studies were included.
Zamborsky & Danisovic L (2020). Surgical Techniques for Knee Cartilage Repair: An Updated Large-Scale Systematic Review and Network Meta-analysis of Randomized Controlled Trials. Arthroscopy: The Journal of Arthroscopic and Related Surgery 36: 845-858.	Systematic review and network meta-analysis n=891 people in n=21 articles (only n=1 RCT examining AMIC with 34 people was included) Follow-up of studies in the meta-analysis ranged from 12 months to 15 years.	Evidence for the glued AMIC arm of the Volz (2017) RCT was entered into a network meta-analysis with other surgical techniques for knee cartilage repair. Compared with microfracture alone (direct comparison) and indirect comparison with matrix induced-ACI, AMIC was better for reintervention rates.	Meta-analyses with more data and focus on AMIC were included. The RCT included in this study was also included in other meta-analyses and in the main evidence.