NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

People with damage to the articular cartilage of the knee (the smooth white tissue covering the ends of the bones) often have pain, catching (a feeling that they cannot move the leg past a certain point), locking and swelling of the knee. This may cause degenerative changes in the joint (osteoarthritis). In this procedure, the damaged articular cartilage inside the knee is removed and tiny holes are drilled through the bone beneath to stimulate the growth of new cartilage. The affected area is then covered with a patch of special material (a microstructural scaffold) for the new cartilage tissue to grow into.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in October 2015.

Procedure name

- Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

Specialist societies

- British Association for Surgery of the Knee.

Description

Indications and current treatment

Chondral damage (or localised damage to the articular cartilage) in the knee can be caused by injury or arthritis, or it can occur spontaneously (a condition called osteochondritis dissecans). It may also happen because of knee instability, muscle weakness, or abnormal unbalanced pressures, for example after an injury to a ligament or meniscal cartilage. In young people the most common cause of cartilage damage is sporting injuries. Symptoms associated with cartilage loss include pain, swelling, instability, joint catching and locking, and may lead to degenerative changes in the joint (osteoarthritis).

There is no uniform approach to managing cartilage defects in the knee. Treatment options depend on the size of the defect and location. There are 2 main categories of procedures: those intended primarily for symptom relief and those that also try to re-establish the articular surface. Interventions that aim to re-establish the articular surface include marrow stimulation techniques (such as abrasion arthroplasty, Pridie drilling and microfracture), mosaicplasty (also known as osteochondral transplantation) and autologous chondrocyte implantation (in which chondrocytes harvested from the knee are cultured and implanted into the damaged cartilage). Interventions that aim to relieve symptoms include knee washout (lavage) with or without debridement, osteotomy, and knee replacement.

What the procedure involves

Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects is done with the patient under general or local anaesthesia, using an open or arthroscopic approach. The damaged articular cartilage is removed and standard bone marrow stimulating procedures, such as microfracturing or Pridie drilling are done. The microstructural scaffold is cut to fit the size of the defect and then fixed into place over the damaged area using, for example fibrin glue, resorbable suture thread or absorbable tacks. The position of the implanted scaffold is checked by bending and extending the knee and the wound is sutured. The aim of this procedure is that the graft or patch ‘captures’ the bone marrow cells and stem cells released by the microfracturing, and acts as a scaffold on which new articular cartilage can grow.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to microstructural scaffold (patch) insertion without autologous cell implantation for

repairing symptomatic chondral knee defects. The following databases were searched,, covering the period from their start to 30.10.2015: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with symptomatic chondral and osteochondral defects in the knee
Intervention/test	Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 289 patients from 1 randomised controlled trial, 7 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

Study 1 Anders S 2013

Details

Study type	**Randomised Controlled Trial**
Country	Germany (2 centres)
Recruitment period	2004–10
Study population and number	n=**38** (**13** autologous matrix-induced chondrogenesis [AMIC]-sutured or **15** AMIC-glued versus **10** microfracture) patients with isolated small- to medium-sized cartilage defects of the knee. Mean defect size 3.4 cm^2 (range 2.1—6.6 cm^2).
Age and sex	Mean age 37 years (range 21–50 years) 81% (31/38) male
Patient selection criteria	Aged 18–50 years, with 1 or 2 cartilage defects of grade III or IV according to the Outerbridge classification and a defect size between 2 cm^2 and 10 cm^2 were included. Patients with more than 2 defects, 2 corresponding defects or defects on both knees, those with signs of osteoarthrosis, bone lesion >0.7 cm and uncorrected knee instability, rheumatoid arthritis, para-infectious or infectious diseases, chronic heart disease, endocrine disease, metabolic disease or autoimmune disease, varus or valgus deformation, previous complete meniscus resection or mosaicplasty, treatment with cartilage specific medication (for example hyaluronic acid) and chondropathia patellae or dysplasia of the patella were excluded.
Technique	Microfracture (MFx) was performed as an arthroscopic procedure. For the Autologous matrix-induced chondrogenesis (AMIC) groups, first MFX was done via a mini-arthrotomy procedure. Then a collagen type I/III matrix (Chondro-Gide) was added to cover the microfactured defect area. This was fixed either using sutures or with fibrin glue. The stable position of the matrix is checked by flexing and extending the knee 10 times. An intra-articular drain without suction was inserted, wound closed and patient hospitalised for 2–5 days. After surgery, a strict postoperative rehabilitation program that included weight bearing and mobilisation exercises, electrotherapy of leg muscles, proprioception, walking, and sports was provided to all patients.
Follow-up	**2 years (n=27)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 8 patients (2 in MFx, 4 in sutured AMIC and 2 in glued-AMIC group) were lost to follow-up at 1 year and 11 patients (4 in MFx, 5 in sutured AMIC and 2 in glued AMIC) were lost to follow-up at 2 years. 1 patient in glued AMIC had a joint replacement after 1 year and dropped out of the efficacy analysis.

Study design issues: study is an interim analysis of an ongoing RCT in which patients were randomised to 1 of 3 study groups by drawing a sealed envelope at arthroscopy. Computer-assisted block randomisation was used. The number in each group was small and varied. Clinical outcomes were evaluated at 1 and 2 years using modified Cincinnati and modified International Cartilage Repair Society (ICRS) scores as well as MRI analysis with emphasis on defect filling. The Modified ICRS Score consists of ratings carried out by the patient and the surgeon, pain and functional status were rated.

Study population issues: 21 patients had previously undergone surgery at the affected knee. Baseline characteristics were comparable between groups.14 patients had injury, 14 had meniscus revision.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30 at 1 year and 27 at 2 years**

Clinical outcomes at 1 and 2 years

	MFx			**Sutured AMIC**			**Glued AMIC**		
	Baseline n=10	**1 year n=8**	**2 years n=6**	**Baseline n=13**	**1 year n=9**	**2 years n=8**	**Baseline n=15**	**1 year n=13**	**2 years n=13**
Modified Cincinnati score* (mean)	37±14	68±17 (p=0.002)	83±8 (p<0.001)	47±20	82±14 (p<0.001)	88±9 (p<0.001)	47.0±15	67±27 (p=0.02)	85±18 (p<0.001)
Pain (mean VAS score)^ [VAS scale 0-no pain, 100-severe pain]	54±21	19±17 (p=0.002)	5±3 (NS)	46±19	14±13 (p< 0.001)	9±6 (NS)	48±20	16±13 (p< 0.001)	10±13 (NS)

The Modified Cincinnati Score is divided into the three parts: assessment of knee function (6–30 points); clinical pathology (0–20 points); and highest activity level without pain (0–50 points) [15]. A maximal score of 100 points is possible. There was no statistical difference between the groups.

Modified ICRS score: Functional status (for all groups)

Patient rated assessment	**1 year, n=30**	**2 years, n=27**
Functional status (according to ICRS Cartilage Injury Standard Evaluation Form-2000 from normal or severely normal)		
Improved	24	12
Stable	6	13
Deteriorated (from normal to nearly normal)	0	2
Surgeon assessment* (knee-related limitation in daily activity)		
Classification of the affected knee (performed using Lachman test, valgus and varus rotation and pivotal shift; each test graded from normal to severely normal)		
Improved	6	1
Stable	24	25
deteriorated		1
Crepitation score		
Improved	10	6
Stable	15	21
Deteriorated	5	0
Functional status		
improved	25	6
stable	3	21
deteriorated (from normal to nearly normal)	5	

*Surgeon-rated assessments found no statistical significances between the groups.

MRI analysis (by independent radiologist; adapted scoring system used)

At 1-year follow-up (n=29), 14 patients showed a defect filling of two-thirds or more. Complete integration was observed in no patient in the MFx group, 2 patients in the sutured-AMIC group and 3 patients in the glued-AMIC group. The quality of the regenerate surface and defect cover; occurrence of bone marrow lesions was comparable between the groups and no further ossification has been observed.

At 2-year follow-up (n=25), defect filling was largely comparable between the groups without statistical significances. Complete integration or with marginal gap was seen in 3 patients in the MFx group, 8 patients in the sutured AMIC and 11 patients in the glued-AMIC group.

Safety

No treatment related adverse events (pain, or impaired motion related to scarring) were reported.

Abbreviations: AMIC, Autologous matrix-induced chondrogenesis; ICRS, International Cartilage Repair Society; MFx, microfracture.

Study 2 Gille J 2013

Details

Study type	**Case series (AMIC registry)**
Country	Germany, Italy, Switzerland.
Recruitment period	2005–13
Study population and number	n=**57** patients with chondral lesions of the knee treated with AMIC Mean defect size of chondral lesions: 3.4 cm^2. Chondral defects Outerbridge classification: Grade III (n=20), IV (n=37). Location of lesions: medial condyle (n=32), lateral condyle (n=6), trochlea (n=4), and at the patella (n=15). Origin: traumatic (n=16), idiopathic (n=41). Previous surgical procedures (n=35): diagnostic arthroscopies (10), partial menisectomies (5), shaving (16), drilling or microfracture (4). Concomitant procedures with AMIC: patella realignment (n=2), corrective osteotomies (n=3), partial menisectomies (n=6), and anterior cruciate ligament reconstruction (n=1). Treated knee: right knee (n=35), left knee (n=22).
Age and sex	Average age 37.3 years (range 17–61 years) 67% (38/57) male
Patient selection criteria	Patients were included in the analysis if they had AMIC treated lesions (grade III or IV) in the knee, enrolled in the AMIC registry since 2005; data available for baseline and specific follow-up times. Those with rheumatic disease, total meniscectomy and revision surgery after the index procedure were excluded from the analysis.
Technique	One-step AMIC procedure with Chondro-Gide performed through a mini-open approach. Fibrin glue used to fix the matrix.
Follow-up	**24 months**
Conflict of interest/source of funding	not reported

Analysis

Follow-up issues: authors state that it was difficult to motivate both patients who are satisfied as well as those with persistent pain to keep the follow-up appointments.

Study design issues: Limited sample size, the registry is a multicentre database that longitudinally tracks changes in function and symptoms using the validated Lysholm score and Visual Analogue Scale (VAS). Patients rated pain using VAS scale with 0 indicating no pain and 10 ‘pain as bad as it could possibly be’. Patients with complete data sets and results were included in the analysis. Radiographic follow-up not done.

Study population issues: heterogeneous population with one or more underlying pathologies.

Other issues: patients from the Gille 2010 study are included in this study.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 57
Clinical outcomes
<table>
<tr><th></th><th>Baseline</th><th>1 year</th><th>2 years</th></tr>
<tr><td>Knee pain (mean VAS, range 0–10)*</td><td>7.0±1.8 (range 1–10)</td><td>2.7±2.4 (range 0–9, p<0.001)</td><td>2.0±2.1
(range 0–9, p=0.003).</td></tr>
<tr><td>Lysholm score (mean)^</td><td>50.1±19.6
(range 9–79)</td><td>79.9±21.2
(range 17–100, p<0.001)</td><td>85.2±18.4
(range 27–100, p=0.002).</td></tr>
</table>
*The mean VAS improvement from baseline to 1 year was 4.2±2.6 (p<0.001), from 1 to 2 years 0.5±2.3 (p=0.003), and from baseline to 2 years 4.7±2.7 (p<0.001).
^The mean improvement from baseline to 1 year was 24.2±31.7 (p<0.001), from 1 to 2 years 11.0±6.1 (p=0.002), and from baseline to 2 years 35.1±19.6 (p<0.001).

Subgroup results: factors that affected clinical outcomes
Age (group A 17–32 years [n=17], group B 33–46 years [n=27], group C 47–65 years [n=13])
Mean Lysholm score improved significantly in all groups at 2 years after surgery (group A: 39.3±20.3, p<0.001; group B: 36.2±21.2, p<0.001; group C: 27.5±11.9, p=0.001). No statistically significant between-group differences from baseline to 2 years were observed (p=0.085).
The mean VAS score also improved significantly in all groups at 2 years after surgery (group A: 5.1±2.0, p<0.001; group B: 5.0±2.6, p<0.001; group C: 3.7±3.2, p=0.003). No statistically significant between-group differences from baseline to 2 years were observed (p=0.338).
Body weight (males with a body weight of more (n=18) or less (n=12) than 90 kg and females with a body weight of more (n=5) or less (n=14) than 70 kg).
Body weight was not found to significantly influence the improvement of the Lysholm score (males 34.2±19.0 and 34.2±12.3, p=0.485; females 42.2±15.6 and 34.9±27.2, p=0.517) or the VAS (males 4.5±2.3 and 6.0±2.4, p=0.068; females 3.8±2.2 and 4.0±2.4, p=0.816) 2 years after surgery.
Defect size (group A: defect size [0–3 cm^2], group B: defect size [3–6 cm^2], group C: defect size [6–9 cm^2]).
The mean outcome improvement measured by the Lysholm and VAS score 2 years after surgery was 34.8±21.1 and 5.0±1.9 in group A, 33.6±17.1 and 4.4±3.4 in group B and 36.4±19.3 and 4.8±2.3 in group C. The between-group results did not differ significantly either in Lysholm (p=0.703) or VAS (p=0.969) scores.
Previous operations (no previous operation (n=22) and previous operations (n=35).
There were no significant differences in Lysholm score improvement (no previous operation: 29.4±19.4; previous operation: 38.7±19.1, p=0.276) and in VAS score (no previous operation: 4.6±2.3; previous operation: 4.9±2.8, p=0.465) at 2 years.
Gender (male and female patients)
There were no significant differences between male and female patients in Lysholm score improvement (female: 36.8±25.9; male: 34.3±15.7, p=0.416) and in VAS score (female: 4.0±2.3; male: 5.1±2.8, p=0.047) at 2 years. For both sexes a significant improvement of Lysholm score and a significant decline of the VAS score were seen at follow-up.</td><td>Authors reported that no complications or adverse events occurred in this case series.</td></tr>
<tr><td colspan="2">Abbreviations used: AMIC, Autologous matrix-induced chondrogenesis; VAS, visual analogue scale.</td></tr>
</table>

Study 3 Gille J 2010

Details

Study type	**Case series (prospective)**
Country	Germany
Recruitment period	2003–05
Study population and number	n=**27** patients with **32** chondral defects of the knee. Mean defect size of chondral lesions: 4.2cm^2 (range 1.3–8.8cm^2) Chondral defects Outerbridge classification: Grade IV 100% Location of lesions: medial femoral condyle (n=7), lateral femoral condyle (n=3), trochlea (n=2), at the patella (n=9) and on the femoral condyle and the patella (n=6). Origin of lesions: traumatic (n=13), idiopathic (n=18) and aseptic necrosis of the subchondral bone (n=1). Previous surgical procedures (n=59): diagnostic arthroscopies (30), partial menisectomies (6), abrasion arthroplasty (9), shaving (9), drilling or microfracture (5). Concomitant procedures with AMIC: patella realignment (n=2), medial capsular shift (=1) Treated knee: right knee (n=16), left knee (n=11).
Age and sex	median age 39 years (range 16-50 years) 59% (16/27) male
Patient selection criteria	Patients with clinical symptomatic chondral lesions grades III-IV according to Outerbridge classification, defect sizes more than 1 cm^2 and defects situated at the femoral condyle, the trochlea or the patella were included. Those with advanced osteoarthritis, significant narrowing of the joint lines, underlying rheumatic disease, total meniscectomy, massive overweight (BMI>35) and deviation of the mechanical axis to the affected compartment were excluded.
Technique	One-step AMIC procedure with Chondro-Gide is performed through a minimal invasive approach. Semi autologous fibrin glue is used to fix the matrix. After surgery, the knee is immobilised for 7 days, followed by continuous passive motion for 6 weeks and non-weight bearing for 6 weeks.
Follow-up	**mean 37 months (between 24 and 62 months)**
Conflict of interest/source of funding	not reported

Analysis

Follow-up issues: follow-up was conducted regularly every 12 months and compared with preoperative findings. 3 patients were excluded from follow-up because of exclusion criteria (1 rheumatoid arthritis, 2 osteoarthritis).

Study design issues: prospective study with small sample size, Outcomes were evaluated using 5 different well established rating systems such as Lysholm score, the Tegner score, the Meyer score, the IRCS score and the Cincinnati score. Two independent observers, blinded to the procedure evaluated all radiographs using the Kellgren–Lawrence scoring system (staging osteoarthritis from grade I to IV). A Kellgren–Lawrence score of greater than or equal to 2 is defined as osteoarthritis. Articular resurfacing and repair was assessed by MRI at end of follow-up, a modified MOCART scoring system was used.

Study population issues: heterogeneous population with one or more underlying pathologies. Concomitant surgical procedures were performed in 3 patients.

Other issues: These patients are included in Gille 2013 study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **27**

Clinical outcomes

	Baseline	1 year	2 years	3 years	4 years
Meyer score (mean)	9±3	14±3	16±3	14±3	NR
Lysholm score (mean)	36±21	67±28	76±24	62±25	47±22
Tegner score (mean)	NR	3.4	4.1	4.0	NR
ICRS (mean)	31±15	59±24	68±22	54±25	37±4
Cincinnati score (mean)	46±18	66±23	74±23	62±26	37±9

Authors reported that significant improvement ($p<0.05$) of all scores was seen at 12 months and further increased values were noted up to 24 months. Non-significant decline in functional scores was seen at a follow-up of 36 months.

Satisfaction with surgery: 87% (20/23) of the patients were highly satisfied with the results after surgery and said they would have the procedure again. 3 patients were not satisfied with their outcome.

Improvement of knee function: an average 89% improvement was reported (on a scale with 0% indicating knee function not allowing daily activities and 100% allowing all activities).

Factors that affect clinical outcomes

Results did not show a significant clinical impact on patient's age. BMI, defect size and number of previous operations. However, male patients showed significant better values in the IRCS score up to 36-month follow-up compared to female patients ($p<0.003$).

MRI analysis after 1 year (n=15)

MRI analysis showed moderate to complete filling (more than 50%) in 10 patients. Bone marrow lesions (in 7 patients), effusion (in 8 patients) and osseous hypertrophy underneath the repair tissue (in 9 patients) were found. A second cartilage defect in another compartment of the same knee joint was seen in 9 patients. Meniscal lesions (in 4 patients) and osteophytes (in 3 patients) have been seen.

3 of the follow-up radiographs showed signs of progressive osteoarthritis (osteophytes, subchondral sclerosis).

Safety

Post-operative complications

Authors reported 2 complications as follows:

Muscle vein thrombosis	1
Effusion after tumbling	1

Authors reported that there were no further negative consequences following treatment of these complications.

Revision surgery was performed in 7.5% (2/27) patients because of symptoms like grinding, catching, pain or swelling after the procedure. Clinical improvement was not seen in these patients.

Abbreviations used: AMIC, Autologous matrix-induced chondrogenesis; ICRS, International Cartilage Repair Society; NR, not reported; VAS, visual analogue scale.

Study 4 Kusano T 2012

Details

Study type	**Case series (retrospective)**
Country	Switzerland
Recruitment period	2003–06
Study population and number	n=**38** patients (**40 knees**) with full-thickness chondral and osteochondral defects of the femoral condyles and patella. Mean defect size of chondral lesions: 3.87 cm^2 Location and type of defect: full-thickness chondral defect of the patella [cP] (n=20), full-thickness chondral defects of the femoral condyle [cF] (n=9), osteochondral defects of the femoral condyle because of osteochondritis dissecans [ocF] (n=11).
Age and sex	Mean age 25.9 years (range 16–50 years) 60% (23/38) male
Patient selection criteria	Patients under 50 years, with isolated chondral or osteochondral lesions on weight-bearing portions of the femoral condyle or the patellofemoral joint, traumatic or atraumatic lesions, grade III–IV, at least 2 cm^2 surrounded with intact cartilage, regardless of limb alignment were included. Patients treated for defects other than the knee were excluded.
Technique	One-step AMIC procedure with Chondro-Gide performed through arthrotomy. The matrix is sutured into the defect and partial autologous fibrin glue is added to improve fixation. In case of osteochondral defect, the bony tissue is removed and the defect is filled with autologous cancellous bone from the iliac crest or tibial metaphysis mixed with hydroxyapatite (Orthoss). The matrix is sutured to the surrounding cartilage and partial fibrin glue is added to improve fixation. Stability of the matrix assessed by extending and flexing the knee. In some cases concurrent surgical procedures (realignment osteotomy in cases of varus or valgus malalignment or patella maltracking with a cartilage lesion of the associated compartment) were performed. Patients are allowed to use crutches and maintain partial weight bearing of 15–20 kg for 6 weeks, passive range of motion after 10 days for 4 weeks (0–60º) and then increase to 90°. Unrestricted weight bearing and range of motion allowed after 6 weeks. If osteotomy is included, full weight bearing delayed until bony consolidation is noted. Physical therapy is given to improve strength and range of motion, patients are allowed to take part in sports after 12 months.
Follow-up	**mean 28.8±1.5 months (13–51 months)**
Conflict of interest/source of funding	not reported

Analysis

Follow-up issues: complete follow-up at a mean of 28 months.

Study design issues: retrospective evaluation with small sample size, a concurrent (realignment or osteotomy) procedure was performed in some cases. Clinical outcomes evaluated before and 12 months after surgery. 4 different scoring systems were used: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form (SKEF); Modified Lysholm knee scoring scale; the Tegner activity score, and a visual analogue scale (VAS). Patient satisfaction was rated on a scale of 0–100% (0 indicating completely dissatisfied and 100 completely satisfied). Radiological outcomes were evaluated on MRI at 12 months according to the MOCART system by a radiologist who was blinded to the clinical outcome. 60% (24/40) knees that had no metallic hardware in place had MRI evaluation. 8 of these were excluded from the analysis because of metal artefact. In the ocF group combination of different materials (Orthoss and MaioRegen) were used in 1-step procedure.

Study population issues: Comparison of preoperative data between the subgroups showed no significant differences with the exception of smaller defect areas in the cF group and decreased age and lower incidence of associated osteotomy in the ocF group.

Other issues: the authors state that reasons for differing findings within the subgroups are not clear.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **38 (40 knees)**

Clinical outcomes

	ocF group (n=11)	cP group (n=20)	cF group (n=9)	p value between groups
IKDC baseline	44±25	51±25	45±26	NS
IKDC follow-up	88±9	74±17	68±14	P=0.0016
p value baseline versus follow-up	p= 0.005	p=0.0025	NS	
Lysholm baseline	50±25	58±17	56±25	NS
Lysholm follow-up	94±8	85±13	76±18	P=0.0158
p value baseline versus follow-up	p=0.0051	p<0.0001	NS	
Tegner baseline	2±2	3±2	4±3	NS
Tegner follow-up	5±2	4±1	4±1	NS
p value baseline versus follow-up	p=0.0115	NS	NS	
VAS baseline	6±3	6±2	6±3	NS
VAS follow-up	1±1	2±2	3±3	p=0.0151
p value baseline versus follow-up	p=0.0048	p=0.0004	NS	
Satisfaction (%)	98±4	84±24	74±43	NS

No significant differences in outcomes were seen when patients treated with AMIC alone were compared with those who had an associated osteotomy or realignment procedure.

Radiological outcomes (MRI analysis and evaluation using MOCART system) (n=16)

Results were inconsistent, with some patients demonstrating a good defect filling while others with no filling or hypertrophy. Integration of the border zone was good but abnormalities of the subchondral bone and lamina were common. All patients demonstrated increased signal in repair tissue.

Safety

Early post-operative complications	% (n)
Haematoma (patient underwent evacuation)	2.5 (1/40)
Knee stiffness (all in the cP group, regained full range of motion after mobilisation under anaesthesia)	22.5 (9/40)

Abbreviations used: AMIC, Autologous matrix-induced chondrogenesis; cP, chondral patella group; cF, chondral femoral condyle group; IKDC, International Knee Documentation Committee; MOCART, magnetic resonance observation of cartilage repair tissue; NS, not significant; ocF, osteochondral femoral condyle group; VAS, visual analogue scale.

Study 5 Kon E 2013

Details

Study type	**Case series (prospective)**
Country	Italy
Recruitment period	not reported
Study population and number	n=**30** patients with chondral or osteochondral knee lesions Location and type of defect: 7 medial femoral condyles, 5 lateral femoral condyles, 11 patellas, 7 trochleas, and 2 tibial plateaus Mean defect size: 2.9±1.3 cm^2 Origin of lesions: traumatic in 5, degenerative in 16, 6 were osteochondritis dissecans Previous surgical procedures: n=19
Age and sex	mean age 34.9 years; 67% (18/27) male
Patient selection criteria	Patients with clinical symptoms such as knee pain or swelling and with International Cartilage Repair Society (ICRS) grade 3–4 chondral and osteochondral lesions of the knee, as evaluated by MRI were included. Patients with absence of meniscal tissue because of total or subtotal meniscectomies, uncorrected axial deviation, or uncorrected knee instability; those with infectious, neoplastic, metabolic, and inflammatory conditions and those not complying with the required postoperative rehabilitation regimen were excluded.
Technique	One-step procedure: Medial or lateral parapatellar arthrotomy is used to expose the osteochondral lesions, defects prepared by removing the sclerotic subchondral bone, MaioRegen (a nanostructured biomimetic scaffold consisting of type I collagen and hydroxyapatite) is implanted using press fit technique. After implantation, early mobilisation and exercises and controlled mechanical compression are performed, partial weight bearing at 4 weeks and full weight bearing at 6 weeks is allowed; low active functional training at 4–6 months and joint impact activities are allowed after 1 year.
Follow-up	**2 years and 5 years**
Conflict of interest/source of funding	One author was a consultant and owned stock in CartiHeal Ltd. One author received research support from Fin-Ceramica Faneza SpA. Scaffolds were supplied by the manufacturer. Study is funded from the European Union's Seventh Framework Programme (FP/2007-13) under grant agreement number 278807.

Analysis

Follow-up issues: 3 patients were lost to follow-up.

Study design issues: prospective study, clinical outcomes assessed using the Cartilage Standard Evaluation Form as proposed by the ICRS, knee function assessed using the International Knee Documentation Committee (IKDC) Knee Examination Form (rated on a 4-point scale 'normal to severely abnormal'); return to sport was assessed with the Tegner score and compared with preoperative and preinjury levels. Imaging evaluation with MRI was also done at 2 years and at a midterm follow-up ranging from 4 to 5 years for 23 lesions. The modified magnetic resonance observation of cartilage repair tissue (MOCART) scoring system was applied for the evaluation of graft maturation. This included a detailed analysis of the subchondral bone status (5 variables, rated on a scale of 1–3). 2 radiologists blindly assessed and reviewed the images in consensus.

Study population issues: heterogeneous group of patients, combined surgery performed in some patients (patients with an axial deviation or an anterior cruciate ligament (ACL) lesion at the time of surgery underwent the combined surgical procedure of realignment or ligament reconstruction during the same surgical session as the scaffold implantation).

Other issues: there might be some overlap with patients in Kon 2014. Both studies were conducted in the same centre in Italy but study periods were not reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **27**

	Before Injury	Preoperative	2 years	5 years
IKDC objective score %		51.8	85.1	92.6 (p<.0005)
Mean IKDC subjective score		40.0±15.0	76.5±14.5 (p<.0005)	77.1±18.0 (p<.0005)
Mean Tegner score	5.2±2.6	1.6±1.1	4.0±1.8 p<.0005)	4.1±1.9 p<0.0005)

Factors that affect clinical outcomes:

Age, BMI, lesion area and site, preinjury activity level, gender, previous or combined surgery, and mechanism of injury did not significantly influence the clinical outcome.

MRI evaluation at 2 and 5 years (n=18, 23 lesions)

MOCART score parameters	2 years	4–5 years
Complete filling of the cartilage (% of lesions)	65.2%	78.3
Complete integration of the graft (% of cases)	69.6	69.6
An intact repair tissue surface (% of cases)	56.5	60.9
A homogeneous structure of the repair tissue (% of cases)	34.8	60.9
An isointense graft signal intensity score with the adjacent native cartilage in dual T2-weighted fast spin echo (% of cases)	34.8	65.2
An isointense graft signal intensity score with the adjacent native cartilage in 3D gradient echo with fat suppression sequences (% of cases)	52.2	69.6
Subchondral lamina considered to be intact (% of cases)	0	4.3
Adhesion (% of cases)	0	0
Effusion (% of cases)	21.7	30.4

The mean total MOCART score showed a statistically significant improvement from 2 years to the midterm follow-up (68.0±13.8 vs 74.8±12.3 respectively; p=.049).

Analysis of subchondral bone status

For the 5 variables evaluated at 2 and 5 years, analysis of the subchondral bone status showed the following respective values:

- bone regeneration level, 2.1±0.8 vs 2.6±0.7 (p=0.008);
- bone signal quality, 1.9±0.7 vs 2.4±0.7 (p =0.005);
- presence of osteophytes or upcoming bone front, 2.7±0.5 vs 2.6±0.7 (NS);
- sclerotic areas surrounding the implant, 2.7±0.5 vs 2.9±0.3 (p=0.08); and
- oedema, 2.3±0.8 vs 2.5±0.8 (NS)

Correlation between imaging and clinical outcomes

No correlations between imaging and clinical findings were observed. Only a tendency towards lower bone quality signal in patients with larger lesions (t=−.456; p=.06) was seen.

Abbreviations used: AMIC, Autologous matrix-induced chondrogenesis; IKDC, International Knee Documentation Committee; MOCART, magnetic resonance observation of cartilage repair tissue; NS, not significant.

Study 6 Kon E 2014

Details

Study type	**Case series (prospective)**
Country	Italy
Recruitment period	Not reported
Study population and number	n=**82** patients with chondral or osteochondral knee lesions Location and type of defect: 41 medial femoral condyles, 26 lateral femoral condyles and 15 trochleas Chondral defects Outerbridge classification: Grade III or IV Mean defect size: 3.2±2.0 cm^2 Origin of lesions: microtraumatic or degenerative in 34, traumatic in 11 and osteochondritis dissecans in 34. Previous surgical procedures: n=50 Concurrent procedures at time of scaffold implantation: n=39
Age and sex	mean age 31.0 years; 80% (63/79) male
Patient selection criteria	Patients with clinical symptoms such as knee pain or swelling and with International Cartilage Repair Society (ICRS) grade 3 to 4 chondral and osteochondral lesions or osteochondritis dissecans located at the femoral condyles or trochlea; those with an axial deviation or anterior cruciate ligament lesion who underwent realignment or ligament reconstruction during scaffold implantation were included. Patients with lesions at the patella or tibial plateaus, or uncorrected misalignment or knee instability; those with infectious, neoplastic, metabolic, and inflammatory conditions and those not complying with the postoperative rehabilitation regimen were excluded.
Technique	One-step procedure: Medial or lateral parapatellar mini arthrotomy was used to expose the osteochondral lesions, defects prepared by removing the sclerotic subchondral bone, MaioRegen (a nanostructured biomimetic scaffold consisting of type I collagen and hydroxyapatite) implanted using press fit technique. After implantation, early mobilisation and exercises and controlled mechanical compression are performed, partial weight bearing at 4 weeks and full weight bearing at 6 weeks is allowed; low active functional training at 4–6 months and joint impact activities are allowed after 1 year.
Follow-up	**1 and 2 years**
Conflict of interest/source of funding	One author was a consultant and owned stock in CartiHeal Ltd. One author received research support from Fin-Ceramica Faneza SpA.

Analysis

Follow-up issues: 3 patients were lost to follow-up.

Study design issues: prospective study with large sample size, clinical outcomes assessed using the Cartilage Standard Evaluation Form as proposed by the ICRS, knee function assessed using the International Knee Documentation Committee (IKDC) Knee Examination Form (rated on a 4-point scale 'normal to severely abnormal'); return to sport was assessed with the Tegner score and compared with preoperative and preinjury levels. Imaging evaluation with MRI was also done at 1 and 2 years. The modified magnetic resonance observation of cartilage repair tissue (MOCART) scoring system was applied for the evaluation of graft maturation. 2 radiologists blindly assessed and reviewed the images in consensus.

Study population issues: heterogeneous group of patients, combined surgery performed in some patients (patients with an axial deviation or an anterior cruciate ligament (ACL) lesion at the time of surgery underwent the combined surgical procedure of realignment or ligament reconstruction during the same surgical session as the scaffold implantation).

Other issues: there might be some overlap with patients in Kon 2013. Both studies were conducted in the same centre in Italy but study periods were not reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **79**

	Before Injury	Preoperative	2 years	5 years
IKDC objective score % (normal and near normal knees)		72.1	88.6 (p=0.024)	p=0.012
Mean IKDC subjective score		47.4±17.1	72.1±18.9 (p<.0005)	76.2±19.6 (p=0.004)
Mean Tegner score	6.3±2.2	2.9±2.0	3.8±1.6 (p<.0005)	4.4±1.9 (p=0.004)

Factors that affect clinical outcomes:

Age, BMI, lesion area and site, preinjury activity level, gender, previous or combined surgery, and mechanism of injury did not significantly influence the clinical outcome.

Patients with OCDs had a higher IKDC subjective score than those with degenerative lesions at 2-year follow-up (p=0.035).

MRI evaluation at 1 and 2 years

MOCART parameters	**2 years n=50 (52 lesions)**	**4-5 years n=43 (45 lesions)**
Complete filling of the cartilage (% lesions)	71.1	62.2
Complete integration of the graft (% cases)	71.1	86.7
An intact repair tissue surface (% cases)	40.4	71.1
A homogeneous structure of the repair tissue (% cases)	42.3	48.9
An isointense graft signal intensity score with the adjacent native cartilage in dual T2-weighted fast spin echo (% cases)	51.9	64.4
An isointense graft signal intensity score with adjacent native cartilage in 3D gradient echo with fat suppression sequences (% cases)	50	62.2
Subchondral bone intact (% cases)	0	33.3
Subchondral lamina considered to be intact (%cases)	0	4.3
Adhesion (% cases)	0	0
Effusion (% cases)	51.9	20

The mean total MOCART score showed a statistically significant improvement between 12 and 24 months.

Correlation between imaging and clinical outcomes

No correlation was found between imaging (MOCART variables) and clinical findings.

Safety

Early post-operative complications	**% (n)**
Swelling (resolved in a few days)	21.5 (17/79)
Joint stiffness (that needed an intervention)-	11 (9/79)

Abbreviations used: AMIC, Autologous matrix-induced chondrogenesis; IKDC, International Knee Documentation Committee; MOCART, magnetic resonance observation of cartilage repair tissue; OCD, osteochondritis dissecans.

Study 7 Delcogliano M 2014

Details

Study type	**Case series (prospective)**
Country	Italy (3 centres)
Recruitment period	2009–11
Study population and number	n=**23** patients with symptomatic knee osteochondritis dissecans (OCD) Location and type of defect: 14 medial femoral condyles, 9 in lateral femoral condyles; grade 3 or 4 of the International Cartilage Repair Society (ICRS). Mean defect size: 3.5±1.43 cm^2
Age and sex	mean age 25.5 years; 83% (19/23) male.
Patient selection criteria	Patients with uncorrected axial malalignment, evaluated clinically and via radiographic examination and those with infectious, neoplastic, metabolic, and inflammatory conditions were excluded.
Technique	Medial or lateral parapatellar arthrotomy is used to expose the osteochondral lesions, defects prepared by removing the sclerotic subchondral bone, MaioRegen (a nanostructured biomimetic scaffold consisting of type I collagen and hydroxyapatite) implanted using press fit technique. After implantation, the stability of the transplant was tested by cyclic flexion extension of the knee; on the second day, early mobilisation and exercises and controlled mechanical compression are performed, partial weight bearing at 4 weeks and full weight bearing at 6 weeks is allowed; low active functional training at 4-6 months and joint impact activities are allowed after 1 year.
Follow-up	**minimum 2 years**
Conflict of interest/source of funding	not reported

Analysis

Follow-up issues: short term but complete follow-up.

Study design issues: prospective study in 3 centres highly specialised in treatment of knee cartilage disorders; clinical outcomes assessed using the ICRS subjective score and knee function assessed using the International Knee Documentation Committee (IKDC) objective score at 12 and 24 months, and every 12 months thereafter; return to sport was assessed with the Tegner score. Imaging evaluation with MRI was also done at 12 and 24 months and every 12 months thereafter. Quality of life was assessed using the EQ-VAS score. Significant differences between baseline line and various follow-up periods were analysed, a p value of less than 0.05 was considered statistically significant.

Study population issues: 13 patients were athletes before symptom onset.

Other issues: it is not clear if there is any overlap with Delcogliano M 2014 (study 8).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **23**

	Pre-injury level	**Baseline**	**1 year**	**2 years**
ICRS subjective score	NR	50.93±20.6	76.44±18.03 (p<0.0005)	82.23±17.36 (p<0.0005)
IKDC objective score %	NR	50	improved	85.1
Mean Tegner score	6.04±1.89	2.34±0.64	NR	5.60±1.72 (p<0.0005)
EQ-VAS score	NR	3.15±1.09	NR	8.15±1.04 (p<0.0005)
Satisfaction % (n)				85

MRI evaluation at 2 years

MRI evaluation showed complete filling of the defect in 80% of the lesions; in 70% of cases the repair tissue was isointense in relation to the adjacent cartilage. In all cases, the scaffold was detectable at the level of the subchondral bone at the 2-year follow-up, producing a different signal with respect to the adjacent subchondral hone.

No cases showed signs of subchondral bone impairment (such as subchondral oedema).

Safety

Adverse events	**% (n)**
Pain and functional limitation of the joints	9(2/23)

Abbreviations used: AMIC, Autologous matrix-induced chondrogenesis; IKDC, International Knee Documentation Committee; ICRS, International Cartilage Repair Society; NR, not reported.

Study 8 Berruto M 2014

Details

Study type	Case series (prospective)
Country	Italy (3 centres)
Recruitment period	2009-11
Study population and number	n=**49** patients with large knee osteochondral lesions. Location and type of defect: 33 medial femoral condyles, 11 in lateral femoral condyles, 4 in tibial plateau and 1 in the trochlea; grade 3 or 4 of the International Cartilage Repair Society (ICRS). Mean defect size: 4.35±1.26 cm^2 (range 3–8.25cm^2); mean depth 6mm. Origin of lesions: OCD n=23, trauma n=10, osteonecrosis=11, idiopathic degeneration n=5. Previous surgical procedures: n=12
Age and sex	mean age 37 years; 76% (37/49) male
Patient selection criteria	patients aged 15–60 years, normal weight, BMI 18–25, Osteochondritis dissecans (OCD) grade 3 or 4, large osteochondral lesions of the femoral condyle, trochlea or the tibial plateau; no mechanical axial deviations or associated surgeries at the time of scaffold implantation were included. Patients who underwent an anterior cruciate ligament reconstruction or high tibial osteotomy as associated surgery were excluded.
Technique	Medial or lateral parapatellar arthrotomy was used to expose the osteochondral lesions, defects prepared by removing the sclerotic subchondral bone, MaioRegen(R) scaffold (a nanostructured biomimetic scaffold consisting of type I collagen and hydroxyapatite) implanted using press fit technique in one-step procedure. After implantation, the stability of the transplant was tested by cyclic flexion extension of the knee; on the second day, early mobilisation and exercises and controlled mechanical compression were performed, partial weight bearing at 4 weeks and full weight bearing at 6 weeks was allowed; low active functional training at 4–6 months and joint impact activities were allowed after 1 year.
Follow-up	**minimum 2 years; 3 year follow (n=30)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: short term follow-up; 30 patients reached 3-year follow-up.

Study design issues: prospective study in 3 centres; clinical outcomes assessed using the International Knee Documentation Committee (IKDC) scores at 12 and 24 months, and every 12 months thereafter; return to sport was assessed with the Tegner score and pain level was graded using a visual analogue scale (VAS). Imaging evaluation with MRI was also done at 12 and 24 months and every 12 months thereafter and evaluated with magnetic resonance observation of cartilage repair tissue (MOCART) scoring scale which has 9 variables to describe the shape and signal intensity of the repaired cartilage compared with adjacent native cartilage. This scale was originally used cartilage lesions and not osteochondral lesions. Significant differences between baseline line and various follow-up periods were analysed, a p value of less than 0.05 was considered statistically significant.

Second look arthroscopy and biopsy was done in 5 patients to investigate persistent knee pain and stiffness after surgery.

Study population issues: 19 patients were competitive athletes before surgery and abandoned sporting activity because of pain. Clinically all patients complained of pain, limited range of motion, recurrent swelling and stiffness.

Other issues: it is not clear if there is any overlap with Delcogliano M 2014 (study 7).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **49**

	preinjury level	**Baseline**	**1 year**	**2 years**	**3 years**	**p value***
Median Tegner score	5.84±1.83	2.20±0.67	NR	4.9±1.73	5.06±1.65	<0.001
Mean VAS	NR	6.69±1.88	2.55±2.38	1.96±2.47	2.1±2.33	<0.005
Mean IKDC subjective score	NR	45.45±19.29	70.86±18.08	75.42±19.31	76.14±18.53	<0.001
Athletes	NR	52.55±20.08	83.21±13.58	86.50±13.20	84.14±15.79	<0.001
Non-athletes	NR	41.34±17.50	61.81±16.17	69.03±19.43	72.75±18.91	<0.001
OCD	NR	50.93±20.60	76.44±18.03	82.23±17.36	80.64±17.09	<0.001
Osteonecrosis	NR	40.54±15.04	65.72±14.83	63.90±19.94	66.11±23.26	<0.001
Mean IKDC subjective score		50% normal and nearly normal knees		89.79% normal and nearly normal		

*postoperative versus 2 year results.

MRI evaluation at 3 years using MOCART scoring scale

MOCART score parameters	**%**
Degree of defect repair and defect filling	70% complete
Integration to border zone	56.6% complete
Surface of the repair tissue	63.3% intact
Structure of the repair tissue	60% homogenous
Signal intensity of the repair tissue	dual T2-FSE 56.6% 3D GE-FS 56.6%
Adhesions	0
Effusion	3.3%

The mean total MOCART score was 63.2±11.7.

Safety

Adverse events	**% (n)**
Bleeding and swelling of knee after surgery (resolved spontaneously within 7 days).	12 (6/49)
Failure because of persistent pain and limited function of knee joint (in 1 patient at 1 year after surgery, patient lost to follow-underwent treatment at another centre; in 2 patients with osteonecrosis of medial femoral condyle 1 patient had unicompartmental knee replacement and 1 had a valgus high tibial osteotomy; in 2 patients with OCD, 1 patient had autologous osteochondral transplantation revision surgery, 1 had a osteochondral allograft transplantation and varus femoral osteotomy).	10 (5/49)

Second look arthroscopy done on failure patients showed subchondral bone exposure in the central part of the defect. Regeneration did not reach the central part.

Abbreviations used: AMIC, Autologous matrix-induced chondrogenesis; IKDC, International Knee Documentation Committee; MOCART, magnetic resonance observation of cartilage repair tissue; OCD, osteochondritis dissecans; NR, not reported.

Efficacy

Clinical outcomes (changes in function and symptoms)

Modified Cincinnati score

In a randomised controlled trial of 38 patients with cartilage knee defects, autologous matrix-induced chondrogenesis (AMIC) techniques, (sutured [n=13] or glued [n=15]) were compared with microfracture (MFx; n=10). In the interim analyses, the mean modified Cincinnati scores (assessing knee function [6–30 points], clinical pathology [0–20 points], and highest activity level without pain [0–50 points]; a maximum possible score of 100 points) increased significantly from baseline values of 47±20 to 82±14 ($p<0.001$) for the sutured-AMIC group, 47±15 to 67±27 ($p=0.02$) for the glued-AMIC group and 37±14 to 68±17 ($p=0.002$) for MFx group respectively at 1-year follow-up. There were no statistically significant differences between the groups. At 2 years, mean scores increased significantly from baseline to 88±9 ($p<0.001$) for the sutured group, to 85±18 ($p<0.001$) for the glued-AMIC group and to 83±8 ($p<0.001$) for MFx group. There were no statistical significant differences between the groups[1].

In a case series of 27 patients with 32 chondral lesions treated with AMIC, the mean Cincinnati scores improved significantly from baseline (46±18 to 66±23; $p<0.05$) at 1 year and further increased to 74±23 at 2 years (level of significance not given). Non-significant declines in scores were seen at 36-month follow-up (62±26) and 48-month follow-up (37±9)[3].

Modified ICRS scores by patient and/or surgeon (rating pain and knee function)

In the randomised controlled trial of 38 patients with cartilage knee defects comparing autologous matrix-induced chondrogenesis (AMIC) techniques, (sutured [n=13] or glued [n=15]) against microfracture (MFx; n=10), at 1-year follow-up, patients in all groups (n=30) rated their functional status as improved (n=24) or stable (n=6) (using the International Cartilage Repair Society [ICRS] Cartilage Injury Standard Evaluation Form-2000. At 2 years, patients in all groups rated their functional status as improved (n=12), remained stable (n=13) or deteriorated (from normal to nearly normal;n=2). Surgeon-rated assessments, based on the modified ICRS score (with respect to functional status, classification of the knee and crepitation using parts 3,4 and 7 of the ICRS form), reported improvement in clinical symptoms and function and found no differences between the groups at 1- and 2-year follow-up[1].

In the case series of 27 patients, mean ICRS scores improved significantly from baseline (31±15 to 59±24; $p<0.05$) at 1 year and further increased (to 68±22) at 2 years (level of significance not given). Scores declined non-significantly at 36-month follow-up (54±25) and 48-month follow-up (37±4)[3].

A case series of 23 patients with symptomatic knee osteochondritis dissecans reported that the ICRS subjective score improved from baseline 50.93±20.6 to 76.44±18.03 at 12 months (p<0.0005) and 82.23±17.36 at 2-year follow-up[7].

International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form scores

In a retrospective case series of 38 patients (40 knees) treated with AMIC for full-thickness chondral and osteochondral defects of the femoral condyles and patella, International Knee Documentation Committee (IKDC) scores (using the IKDC Subjective Knee Evaluation form 2000,summing the scores for individual items and them transforming the score to a scale that ranges 0–100, higher scores representing higher levels of function and lower levels of symptoms) improved significantly from baseline to a mean follow-up of 28.8 months in the osteochondral femoral condyle group (from 44±25 to 88±9, p=0.005) and the chondral patella group (from 51±25 to 74±17, p=0.0025). However, improvements in the chondral femoral condyle group were not significant (from 45±26 to 68 ±14). Significant differences were seen between the 3 groups (p=0.0016). There were no significant differences in outcomes in patients treated with AMIC alone compared with those who also had an osteotomy or realignment procedure[4].

In a case series of 30 patients treated for chondral or osteochondral lesions with a cell free collagen hydroxyapatite osteochondral scaffold, mean IKDC subjective scores improved significantly from 40.0±15.0 at baseline to 76.5±14.4 (p<0.0005) at 2-year follow-up and 77.1±18.0 (p<0.0005) at 5-year follow-up[5].

A case series of 49 patients treated with a biomimetic scaffold for large osteochondral lesions reported that the IKDC subjective score improved from a mean score of 45.45±19.29to 70.86±18.08 at 12-month follow-up. A further improvement was reported at 24 months (mean score 75.42±19.31, p<0.001)[8].

Lysholm score

A case series of 57 patients with chondral lesions of the knee treated with AMIC reported significant improvement of the mean Lysholm score (a patient' knee functional scoring scale with 8 items and a maximum possible score of 100) from baseline value of 50.1±19.6 to 79.9±21.2 at 1-year follow-up and further increase to 85.2±18.4 at 2-year follow-up. The mean improvement from baseline to 1 year was 24.2±31.7 (p<0.001), from 1 to 2 years 11.0±6.1 (p=0.002), and from baseline to 2 years 35.1±19.6 (p<0.001)[2].

In the case series of 27 patients, mean Lysholm score improved significantly from baseline (36±21 to 67±28; p<0.05) at 1-year follow-up and further increase to 76±24 at 2-year follow-up (level of significance not given). Non-significant declines in scores were seen at 36-months follow-up (62±25) and 48-month follow-up (47±22)[3].

The retrospective case series of 38 patients (40 knees) treated with AMIC reported significant improvement in Lysholm scores from baseline scores to a mean follow-up of 28.8 months in the osteochondral femoral condyle group (from 50±25 to 94±8, p=0.0051) and the chondral patella group (from 58±17 to 85±13, p<0.0001). However, improvements in the chondral femoral condyle group were not significant (from 56±25 to 76±18). Significant differences were seen between the 3 groups (p=0.0158). No significant differences in outcomes were seen when patients treated with AMIC alone were compared with those who had an associated osteotomy or realignment procedure[4].

Meyer score

In the case series of 27 patients, mean Meyer score (not defined in paper) improved significantly from baseline (9±3 to 14±3; p<0.05) at 1-year follow-up and further improved to 16±3 at 2 years (level of significance not given). Non-significant decline in mean scores was seen at 36-month follow-up (14±3)[3].

Tegner score

In the case series of 27 patients, mean Tegner score (a patient' activity level scale, score range 0–10, with higher scores representing participation in higher-level activities) improved from baseline (not reported) to 3.4 (p<0.05) at 1-year follow-up and further increased to 4.1 at 2-year follow-up (level of significance not given). Non-significant decline in scores was seen at 36-month follow-up (4.0)[3].

The retrospective case series of 38 patients (40 knees) reported significant improvement in Tegner scores from baseline scores to a mean follow-up of 28.8 months in the osteochondral femoral condyle group (from 2±2 to 5±2, p=0.0115). However, improvements in the chondral patella group and the chondral femoral group were not significant (3±2 to 4±1; 4±3 to 4±1). There were also no significant differences between the 3 groups[4].

In the case series of 30 patients with chondral or osteochondral lesions treated with a cell free collagen hydroxyapatite osteochondral scaffold, mean Tegner score improved significantly from 1.6±1.1 at baseline to 4.0±1.8 (p< 0.0005) at 2-year follow-up and to 4.1±1.9 (p< 0.0005) at 5-year follow-up[5].

In the case series of 23 patients with symptomatic knee osteochondritis dissecans Tegner Activity score showed a significant increase from 2.34±0.64 to 5.60±1.72 at 2-year follow-up[7].

EQ-VAS score

In a case series of 23 patients with symptomatic knee osteochondritis dissecans, EQ-VAS score (a measure of patients' own global rating of their overall health, on a scale 0 [worst imaginable health state] to100 [best imaginable health state] had improved significantly from baseline at 2-year follow-up (3.15±1.09 to 8.15±1.04; p<0.0005)[7].

Pain and knee function on Visual Analogue Scale

In the randomised controlled trial of 38 patients with cartilage knee defects comparing autologous matrix-induced chondrogenesis (AMIC) techniques, (sutured [n=13] or glued [n=15]) against microfracture (MFx; n=10), pain (measured on a visual analogue scale [VAS], 0 [no pain] to100 [severe pain]) was rated less severe at 1- and 2-year follow-up compared with baseline and was comparable between the groups. At 1-year follow-up, pain decreased significantly from baseline for sutured AMIC (46±19 to 14±13; p<0.001), for glued AMIC (48±20 to 16±13; p<0.001) and MFx (54±21 to 19±17; p=0.002), and was further reduced at 2-year follow-up without statistical significance (9±6 for sutured AMIC, 10±13 for glued AMIC, 5±3 for MFx)[1].

In a case series of 57 patients, knee pain (measured with VAS) improved significantly from baseline at 1 year follow-up (7.0±1.8 to 2.7± 2.4; p<0.001) and at 2-year follow-up (2.0± 2.1; p<0.003). The mean VAS improvement from baseline to 1-year follow-up was 4.2±2.6 (p<0.001), from 1- to 2-year follow-up was 0.5±2.3 (p=0.003), and from baseline to 2-year follow-up was 4.7±2.7 (p<0.001)[2].

The case series of 38 patients (40 knees) reported significant improvement in VAS scores from baseline scores to a mean follow-up of 28.8 months in the osteochondral femoral condyle group (from 6±3 to 1±1, p=0.0048) and the chondral patella group (from 6±2 to 2±2, p=0.0004). However, improvements in the chondral femoral condyle group were not significant (from 6±3 to 3±3). Significant differences were seen between the 3 groups (p=0.0151)[4].

The case series of 27 patients reported an average 89% improvement in knee function (on a scale with 0% indicating knee function not allowing daily activities and 100% allowing all activities)[3].

Patient satisfaction

The case series of 27 patients treated with AMIC reported that 87% (20/23) of patients were highly satisfied with the results after surgery and said they would undergo the procedure again. 3 patients were not satisfied with their outcome[3].

In the case series of 38 patients (40 knees) patient satisfaction (rated on a scale of 0–100%, 0 indicating completely dissatisfied to 100 indicating completely satisfied) was high in all subgroups and there was no significant difference between groups (osteochondral femoral group 98±4; chondral patella group 84±24; chondral femoral condyle group 74±43)[4]. In the case series of 23 patients with symptomatic knee osteochondritis dissecans satisfaction was recorded in 85% (absolute numbers not given) of patients[7].

Imaging results (radiological and/or MRI evaluation)

In the RCT of 38 patients, MRI assessment by an independent radiologist using an adapted scoring revealed a satisfactory and homogenous defect filling in the majority of patients[1].

The case series of 27 patients treated with AMIC reported that MRI analysis after 1 year in 15 patients showed moderate to complete filling (more than 50%) with a normal to incidentally hyperintense signal in most cases in 10 patients. Bone marrow lesions (n=7), effusion (n=8) and osseous hypertrophy underneath the repair tissue (n=9) were found. A second cartilage defect in another compartment of the same knee joint was seen in 9 patients. Meniscal lesions (4) and osteophytes (3) have been seen in some knees. Three of the follow-up radiographs showed signs of progressive osteoarthritis (osteophytes, subchondral sclerosis)[3].

The case series of 38 patients (40 knees) reported that MRI evaluation (using MOCART system in 15 patients) showed that the results were inconsistent, with some patients demonstrating a good defect filling while others with no filling or hypertrophy. Integration of the border zone was good but abnormalities of the subchondral bone and lamina were common. All patients demonstrated increased signal in repair tissue[4].

In the case series of 30 patients with chondral or osteochondral lesions treated with a cell free collagen hydroxyapatite osteochondral scaffold, MRI evaluation showed an improvement in both the MOCART score and subchondral bone status (part of MOCART, 5 variables rated on a scale of 1–3) at 2- and 5-year follow-up. At 5-year follow-up, complete filling of the cartilage was shown in 78% of lesions (absolute numbers not given), complete integration of the graft was detected in 70% of cases, the repair tissue surface was intact in 61% of cases and the structure of the repair tissue was homogenous in 61% of the cases. No correlation was found between MRI findings and clinical outcome[5].

Safety

Haematoma

Haematoma after the autologous matrix-induced chondrogenesis (AMIC) procedure, developed in 1 patient in a case series of 38 patients (40 knees) with full-thickness chondral and osteochondral defects of the femoral condyles and patella. The haematoma was excavated[4].

Muscle vein thrombosis

Muscle vein thrombosis was reported in 1 patient in the case series of 27 patients. This complication resolved after treatment[3].

Effusion

Effusion ‘after tumbling’ was reported in 1 patient in the case series of 27 patients. This complication resolved after treatment[3].

Knee stiffness

Knee stiffness was reported in 22% (9/40) patients in the case series of 38 patients (40 knees) after the procedure. This was reported in patients in chondral patella group. Patients regained full range of motion after mobilisation under anaesthesia[4].

Re-intervention

Revision surgery was carried out in 8% (2/27) of patients because of grinding, catching, pain or swelling after the procedure. Clinical improvement was not seen in these patients[3].

Revision surgery, because of pain and limited function of the knee, was carried out in 10% (5/49) of patients in a case series of 49 patients with large osteochondral knee lesions treated with a biomimetic osteochondral scaffold. In 2 patients with osteonecrosis of medial femoral condyle, unicompartmental knee replacement was done in 1 patient and a valgus high tibial osteotomy was done in the other patient. In 2 patients with OCD, autologous osteochondral transplantation revision surgery was done in 1 patient and osteochondral allograft transplantation and varus femoral osteotomy was done in the other patient. The fifth patient, who lost to follow-up, had treatment at another centre[8].

Bleeding

Bleeding and swelling of the knee after surgery was reported in 12% (6/49) of patients in a case series of 49 patients all of which resolved spontaneously within 1 week[8].

Swelling

Swelling, which resolved in a few days was reported in 22% (17/79) of patients in a case series of 82 patients[6].

Validity and generalisability of the studies

- Only 1 prospective, randomised trial is compared AMIC against microfracture.
- Modified AMIC techniques (called AMIC plus technique) are out of the scope of this guidance.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Mosaicplasty for knee cartilage defects. NICE interventional procedure guidance 162 (2006). Available from http://www.nice.org.uk/guidance IPG162
- Partial replacement of the meniscus of the knee using a biodegradable scaffold. NICE interventional procedure guidance 430 (2012). Available from http://www.nice.org.uk/guidance IPG430
- Arthroscopic radiofrequency chondroplasty for discrete chondral defects of the knee. NICE interventional procedure guidance 493 (2014). Available from http://www.nice.org.uk/guidance IPG493

Technology appraisals

- The use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints. NICE technology appraisal 89 (2005). Available from http://www.nice.org.uk/guidance/TA89
- Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)). [Not yet published].

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Specialist Advisor Questionnaire for microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects was submitted and can be found on the NICE website [update HYPER LINK with IP number on publication].

Patient commentators' opinions

NICE's Public Involvement Programme sent xxx questionnaires to xxx NHS trusts for distribution to patients who had the procedure (or their carers). NICE received xxx completed questionnaires.

Section to be inserted if there is no patient commentary

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Section to be inserted if patient commentators raised no new issues

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Section to be inserted if patient commentators raised new issues

The patient commentators raised the following issues about the safety/efficacy of the procedure, which did not feature in the published evidence or the opinions of specialist advisers, and which the Committee considered to be particularly relevant:

- [insert additional efficacy and safety issues raised by patient commentators and highlighted by IPAC, add extra rows as necessary].
- [Last item in list].

Issues for consideration by IPAC

- Ongoing trials
  - NCT01458782: A Randomised Trial Comparing Autologous Chondrocyte Implantation Using Collagen Membrane (ACI-C-Chondro-Gide) Versus (Autologous Matrix Induced Chondrogenesis-Chondro-Gide) AMIC for Repair of Cartilage Defects in the Knee. Phase II, n=80; primary outcome:

Perceived treatment efficacy as change from baseline in KOOS score; location: Norway; estimated completion date: October 2014.

- NCT01282034: Multicentre randomised controlled trial for the treatment of knee chondral and osteochondral lesions: marrow stimulation techniques (drilling or microfractures) vs MaioRegen surgery (phase 4); n=150; primary outcome: IKDC Subjective Knee Evaluation Score; location: international 10 centres; estimated trial completion: June 2015.
- NCT02345564: Clinical and Radiological Results of Osteochondral Repair Using MaioRegen in Knee and Ankle Surgery; interventional single group study; n=15; primary outcome: MRI imaging - gap between cartilage-implant surface in mm (ingrowth of fleece into the cartilage); estimated completion date December 2015.

References

1. Anders S, Volz M et al (2013). A Randomized, Controlled Trial Comparing Autologous Matrix-Induced Chondrogenesis (AMIC) to Microfracture: Analysis of 1- and 2-Year Follow-Up Data of 2 Centers. The Open Orthopaedics Journal 7 133-143.
2. Gille J, Behrens P et al (2013). Outcome of Autologous Matrix Induced Chondrogenesis (AMIC) in cartilage knee surgery: data of the AMIC Registry. Archives of Orthopaedic & Trauma Surgery 133 (1) 87-93.
3. Gille J, Schuseil E et al (2010). Mid-term results of Autologous Matrix-Induced Chondrogenesis for treatment of focal cartilage defects in the knee. Knee Surgery, Sports Traumatology, Arthroscopy 18 (11) 1456-1464.
4. Kusano T, Jakob RP et al (2012).Treatment of isolated chondral and osteochondral defects in the knee by autologous matrix-induced chondrogenesis (AMIC). Knee Surgery, Sports Traumatology, Arthroscopy 20 (10) 2109-2115.
5. Kon E, Filardo G et al (2013). Clinical results and MRI evaluation of a nano-composite multi-layered biomaterial for osteochondral regeneration at 5 years. The American Journal of Sports Medicine. 42 (1), 158-165.
6. Kon E, Filardo G et al (2014). A one step treatment for chondral and osteochondral knee defects: clinical results of a biomimetic scaffold implantation at 2 years of follow-up. Journal of Materials Science: Materials in Medicine. 25:2437-2444
7. Delcogliano M, Menghi A et al (2014). Treatment of osteochondritis dissecans of the knee with a biomimetic scaffold. A prospective multicenter study. Joints. 2 (3): 102-8
8. Berruto M, Delcogliano M et al (2014). Treatment of large knee osteochondral lesions with a biomimetic scaffold. The American Journal of Sports Medicine. 22, 7: 1607-1617.

Appendix A: Additional papers on microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
BarkS, Piontek T, et al (2014). Enhanced microfracture techniques in cartilage knee surgery: Fact or fiction?. [Review]. World Journal of Orthopedics 5 (4) 444-449.	This article reviews the pre-clinical rationale of microfractures and autologous matrix-induced chondrogenesis (AMIC), presents clinical studies and shows the advantages and disadvantages of these widely used techniques.	Both cartilage repair techniques represent an effective and safe method of treating full-thickness chondral defects of the knee in selected cases. While results after microfracture deteriorate with time, mid-term results after AMIC seem to be enduring. Randomized studies with long-term follow-up are needed whether the grafted area will maintain functional improvement and structural integrity over time.	Review.
Becher C, Ettinger M et al (2015). Repair of retropatellar cartilage defects in the knee with microfracture and a cell-free polymer-based implant. Archives of Orthopaedic & Trauma Surgery 135 (7) 1003-1010.	Case series n=5 Symptomatic retropatellar cartilage defects covered with microfracturing and Chondrotissue implant immersed with autologous serum. Follow-up: mean 21 months (range 11-31 months)	MRI showed good to excellent defect fill with complete integration. The mean MOCART score was 61 (range 50-75) points. The mean Henderson score was 7 (range 6-9) points. All patients showed subchondral bone alterations. The KOOS showed good values in all sub-categories in 4 out of 5 patients and a mean overall score of 73 (range 40-90) points. Two patients rated the outcome as excellent, two as good and one as fair. All patients would have the procedure again and recommend it.	AMIC plus technique.
Behery O, Siston RA et al (2014). Treatment of cartilage defects of the knee: expanding on the existing algorithm. [Review]. Clinical	Systematic review 27 studies (1450 human and 50 animal subjects)	Female sex and higher BMI significantly predicted cartilage loss rates and recovery after microfracture (MFx) and AMIC. Defect size and location	Factors affecting cartilage treatment and outcomes. General review.

Journal of Sport Medicine 24 (1) 21-30.		significantly predicted treatment outcomes. Sizes >2 to 4 cm demonstrated worse outcomes after MFx treatment. Defect size did not consistently affect ACI or osteochondral autograft transplantation outcomes. Intra-articular lesion location was related to intralesional subchondral bone contact and MFx outcome. Corrected patellofemoral and tibiofemoral alignment improved clinical outcome when realignment procedures were done concurrently with cartilage repair.	
Benthien JP and Behrens P (2010). Autologous Matrix-Induced Chondrogenesis (AMIC): Combining Microfracturing and a Collagen I/III Matrix for Articular Cartilage Resurfacing. Cartilage 1 (1) 65-68.	This article describes the new method of autologous matrix-induced chondrogenesis (AMIC), a 1-step procedure combining subchondral microfracture with the fixation of a collagen I/III membrane by a partially autologous fibrin glue.	Indications and contraindications are provided; a technical note is given. This method is primarily applied in osteochondral lesions of the knee and ankle joints; other joints may qualify.	Describes technique.
Benthien JP and Behrens P (2011). The treatment of chondral and osteochondral defects of the knee with autologous matrix-induced chondrogenesis (AMIC): method description and recent developments. Knee Surgery, Sports Traumatology, Arthroscopy 19 (8) 1316-1319.	Technical note describes the method of autologous matrix-induced chondrogenesis (AMIC), a one-step procedure combining subchondral microfracture with the fixation of a collagen I/III membrane with fibrin glue or sutures.	This method is applied primarily in chondral or osteochondral lesions of the knee. Indications and contraindications are provided; the technique is described. The further development of AMIC is described with an increased focus on the subchondral zone and the complex of cartilage and bone, the osteochondral unit, which receives increased attention in cartilage research.	Technical note on AMIC and its further development.
Christensen BB, Foldager CB et al (2015). Poor osteochondral repair by a biomimetic collagen scaffold: 1- to 3-year clinical and radiological follow-up. Knee Surg, Sports Traumatol Arthrosc.	Case series (prospective cohort study) n=10 patients with osteochondral lesions (knee 6, talus 4) treated with MaioRegen scaffold (a cell-free biomimetic scaffold consisting of type I collagen and hydroxyapatite) Follow-up: 2.5 years	2 patients were re-operated and excluded from further follow-up due to treatment failure. None of the patients had complete regeneration of the subchondral bone evaluated using CT. At 2.5 years, 6/8 patients had no or very limited (<10 %) bone formation in the defects and 2/8 had 50-75 % bone formation in the treated defect. MRI showed no improvement in the MOCART score at any time	Results not reported separately for different injury locations (knee and ankle). Larger studies with longer follow-up included in table 2.

		point. The IKDC score improved from 41.3 to 80.7, and the KOOS pain subscale improved from 63.8 to 90.8 at 2.5-year follow-up. No improvement was found with the remaining KOOS subscales, the Tegner or AOFAS Ankle-Hindfoot score.	
Cuellar R, Cuellar A et al (2014). Arthroscopic technique for the treatment of patellar chondral lesions with the patient in the supine position. Arthroscopy Techniques 3 (3) e373-e376.			Describes technique for AMIC.
Dewan AK, Gibson MA et al (2014). Evolution of autologous chondrocyte repair and comparison to other cartilage repair techniques. [Review]. BioMed Research International 2014 272481.		Microfracture, abrasion chondroplasty, osteochondral grafting, ACI, and autologous matrix-induced chondrogenesis are distinguishable by cell source (including chondrocytes and stem cells) and associated scaffolds (natural or synthetic, hydrogels or membranes). ACI seems to be as good as, if not better than, microfracture for repairing large chondral defects in a young patient's knee as evaluated by multiple clinical indices and the quality of regenerated tissue.	Review on evolution of ACI and other cartilage repair techniques.
Delcogliano M, de Caro F et al (2014). Use of innovative biomimetic scaffold in the treatment for large osteochondral lesions of the knee. Knee Surgery Sports Traumatology Arthroscopy. 22:1260-69.	Case series n=21 patients with osteochondral lesions Implantation of a biomemtic scaffold. Follow-up: 2 years	The IKDC subjective score improved from a mean score of 35.7±6.3 at baseline to 67.7±13.4 at 12-month follow-up ($p<0.0005$). A further improvement was documented from 12 to 24 months (mean score of 72.9±12.4 at 24 months) ($p<0.0005$). The IKDC objective score confirmed the results. The Tegner activity score improvement was statistically significant ($p<0.0005$). The EQ-VAS showed a significant improvement from 3.15±1.09 to 7.35±1.14 ($p<0.0005$) at 2-year follow-up.	Larger and longer follow-up studies included in table 2.
Dhollander A A, De	Case series	A clinical improvement	AMIC plus technique

Neve F, Almqvist KF et al (2011). Autologous matrix-induced chondrogenesis combined with platelet-rich plasma gel: technical description and a five pilot patients report. Knee Surgery, Sports Traumatology, Arthroscopy 19 (4) 536-542.	n=5 Autologous matrix-induced chondrogenesis (AMIC) combined with platelet-rich plasma gel, the so called AMIC plus technique, for the treatment of patellar cartilage defects in the knee. Follow-up: 2 years	became apparent after 24 months of follow-up. Both MOCART scoring systems revealed no significant deterioration or improvement of the repair tissue between one and 2 years of follow-up. However, all cases showed subchondral lamina and bone changes. The formation of intralesional osteophytes was observed in 3 of the 5 patients during the 2 years of follow-up.	
Dhollander A, Moens K. et al (2014). Treatment of patellofemoral cartilage defects in the knee by autologous matrix-induced chondrogenesis (AMIC). Acta Orthopaedica Belgica 80 (2) 251-259.	Case series n=10 patients with patellofemoral cartilage defects in the knee treated with autologous matrix-induced chondrogenesis (AMIC) (Chondro-Gide) Follow-up: 2 years	A satisfying clinical improvement became apparent during the 24 months of follow-up. The MOCART scoring system revealed a slight tendency to deterioration on MRI between one and 2 years of follow-up. However, the difference was not statistical significant. All cases showed subchondral lamina changes. The formation of intralesional osteophytes was observed in 3 of the 10 patients (30%). No infections occurred, 2 patients (20%) underwent a second look arthroscopy because of catching, revealing hypertrophy of the regenerated tissue, which was treated by shaving.	Larger and longer follow-up studies included in table 2.
de, Girolamo ,L Quaglia A et al (2012). Modified autologous matrix-induced chondrogenesis (AMIC) for the treatment of a large osteochondral defect in a varus knee: a case report. Knee Surgery, Sports Traumatology, Arthroscopy 20 (11) 2287-2290.	Case report n=1 patient affected by a large osteochondral defect of the medial femoral condyle (6 cm(2)) in a varus knee treated with a combined approach consisting of high tibial osteotomy and autologous matrix-induced chondrogenesis technique enhanced by a bone marrow-enriched bone graft.	Twelve months after surgery, the patient reported considerable reduction in pain and significant increase in his quality of life. A hyaline-like cartilage completely covered the defect and was congruent with the surrounding condyle cartilage as revealed by MRI and by a second-look arthroscopy.	AMIC plus technique
Jacobi M, Ronn K, Wahl, P, and Gautier E (2010). Treatment of isolated cartilage lesions of the knee. Current Rheumatology Reviews.6 (1) (pp 72-76),		Many surgical techniques (debridement, stimulation by microfracture, mosaicplasty, autologous chondrocyte implantation (ACI) and autologous matrix-induced chondrogenesis (AMIC)) have been undertaken for biological repair of the	Review

		cartilage surface. Although these treatments are promising, there is no evidence for a breakthrough in cartilage repair. It justifies cartilage repair procedures in patients with symptomatic full-thickness lesions and in patients with large defects in the weight bearing surface of the knee joint.	
Gobbi A, Karnatzikos G et al (2011). One-Step Cartilage Repair with Bone Marrow Aspirate Concentrated Cells and Collagen Matrix in Full-Thickness Knee Cartilage Lesions: Results at 2-Year Follow-up. Cartilage 2 (3) 286-299.	Case series prospective n=15 patients with grade IV cartilage lesions of the knee. All patients underwent a mini-arthrotomy and concomitant transplantation with BMAC (Bone marrow aspirate concentrated) covered with the collagen matrix. Bone marrow was harvested from ipsilateral iliac crest and subjected to concentration and activation with Batroxobin solution. This clot was implanted into the prepared cartilage defect, and then covered with ChondroGide. Follow-up: 2 years	Patients showed significant improvement in all scores at final follow-up ($P < 0.005$). Patients presenting single lesions and patients with small lesions showed higher improvement. MRI showed coverage of the lesion with hyaline-like tissue in all patients in accordance with clinical results. Hyaline-like histological findings were also reported for all the specimens analysed. No adverse reactions or postoperative complications were noted.	AMIC combined with BMAC (BMAC (autologous bone marrow concentrate) and collagen scaffold (ChondroGide) are used in 1 step procedure). Combination of different materials in 1 step procedure.
Buda R, Vannini F (2013). One-step arthroscopic technique for the treatment of osteochondral lesions of the knee with bone-marrow-derived cells: three years results. Musculoskeletal Surgery 97 (2) 145-151.	Case series n=30 patients with osteochondral lesions of the knee. 1 step arthroscopic procedure – bone marrow harvested from patient's iliac crest and arthroscopically implanted with a scaffold into the lesion site. Follow-up: 3 years	Mean International Knee Documentation Committee (IKDC) score before surgery was 29.9 +/- 13.2 and 85.4 +/- 4.2 at 29 +/- 4.1 months ($p < 0.0005$), while Knee injury and Osteoarthritis Outcome Score (KOOS) before surgery was 35.1 +/- 11.9 and 87.3 +/- 7.3 at 29 +/- 4.1 months ($p < 0.0005$). Control MRI and bioptic samples showed an osteochondral regeneration of the lesion site. The one-step technique appears to be a good and reliable option for treatment of OLK at three years of follow-up.	AMIC combined with BMAC.
Buda R, Vannini F et al (2010). Osteochondral lesions of the knee: new one step repair technique with bone	Case series n=20 Follow-up: 24 months	No complications observed. The mean IKDC score was 32.9 at baseline and 90.4 at a mean follow-up of 29 months ($p<0.0005$). While	AMIC combined with BMAC.

marrow derived cells. Journal of Bone and Joint Surgery Am. 92 (Suppl 2) 2-11.	No drilling, Hylofast PRP BMAC.	the KOOS SCORE was 47.1 at baseline 93.3 at a mean follow-up 29 months (P<0.0005).	
Kon E, Delcogliano M et al (2009). Novel nano-composite multi-layered biomaterial for the treatment of multifocal degenerative cartilage lesions. Knee Surgery Sports Traumatology, Arthroscopy 17: 1312-15.	Case report n=1, 46 year old patient with large degenerative chondral lesions of the medial femoral condyle, trochlea and patella. Treated with a closing-wedge high tibial osteotomy and implant of a biomimetic nanostructured osteochondral bioactive scaffold (MaioRegen-Fin- Ceramica S.p.A., Faenza, Italy). Follow-up: 1 year.	No complications occurred. After 1 year of follow-up the patient was pain-free, had full knee range of motion, and had returned to his pre-operation level of athletic activity. MRI evaluation at 6 months showed that the implant gave a hyaline-like signal as well as a good restoration of the articular surface, with minimal subchondral bone oedema. Subchondral oedema progressively decreased and was almost non-visible at 12 months.	AMIC combined with high tibial osteotomy. Larger and longer follow-up studies included in table 2.
Kon E, Delcogliano M et al (2009). A novel nano-composite multi-layered biomaterial for treatment of osteochondral lesions: Technique note and an early stability pilot clinical trial. Injury 41, 7, 693-701.	Case series(prospective) n=13 patients (15 defects-4 medial femoral condyle, 2 lateral femoral condyle, 5 patella, 4 at troachleas). Mean defect size: 2.8 cm^2. Implantation of a biomimetic osteochondral scaffold (MaioRegen). Follow-up: 25-26 weeks	A completely attached graft in 86.7% (13/15), partial detachment in 13.3% (2/15) was observed. At 6 months, with MRI evaluation, complete filling of the cartilage defect and congruency of the articular surface were seen in 66.7% (10/15) lesions. Complete integration of the grafted cartilage was detected in 53.3% (8/15) lesions. Subchondral bone changes (oedema or sclerosis) were found in 53.3% (8/15) lesions. Significant improvement in the International Knee Documentation Committee (IKDC) subjective and objective scores from preoperative to 6 months' follow-up ($p < 0.0005$) was seen. Visual scoring of the repaired tissue revealed a normal repair score in one case and a near-normal repair score in the other case. Histological analysis showed the formation of subchondral bone without the presence of biomaterial.	Larger and longer follow-up studies included in table 2.
Kon E, Delcogliano M et al (2011). Novel nano-composite multi-layered biomaterial for osteochondral regeneration: a pilot clinical trial. American J	Case series n=30 patients with knee chondral and osteochondral lesions treated with MaioRegen scaffold.	The Tegner and International Knee Documentation Committee objective and subjective scores improved significantly from the baseline evaluation to the 6,	Pilot study Same study with longer follow-up included in table 2.

Sports Med 39(6): 1180-1190.	Follow-up; 2 years	12, and 24-month follow-ups. Further analysis showed a slower recovery but same results for patients who presented with adverse events, for older patients, for patients who underwent previous surgery, and for those with patellar lesions. In contrast, a faster recovery was observed in active patients. At MRI evaluation, complete filling of the cartilage and complete integration of the graft was shown in 70% of the lesions. However, the subchondral lamina and bone were considered intact in a minority of cases (7% and 47%, respectively).	
Kon E, Filardo G et al (2014).Tibial plateau lesions. Surface reconstruction with a biomimetic osteochondral scaffold: Results at 2 years of follow-up. Injury 45 Suppl-5.2014.	Case series n=11 patients with osteochondral lesions of the tibial plateau treated with MaioRegen scaffold. Follow-up: 2 years	Three patients experienced minor adverse events. No patients required further surgery for treatment failure during the study follow-up period, and 8 patients (72.7%) reported a marked improvement. The IKDC subjective score improved from 42.5±10.2 before treatment to 69.8±19.0 at 12 months ($p < 0.05$), with stable results at 24 months. The IKDC objective score increased from 27.3% normal and nearly normal knees before treatment to 85.7% normal and nearly normal knees at 24 months of follow-up. The Tegner score increased from 2.3±2.1 before treatment to 4.8±2.4 at 12 months ($p < 0.05$), and was stable at the final follow-up.	Studies with longer follow-up included in table 2.
Filardo G, Kon E, Di Martino A et al (2013). Treatment of knee osteochondritis dissecans with a cell free biomimetic osteochondral scaffold: clinical and imaging evaluation at 2 year follow-up. Am J sports Med. 41 (8), 1786-93.	Case series n=27 patients with symptomatic knee OCD of the femoral condyles (Grade 3 or 4, average defect size 3.4 cm2) treated with the implantation of a 3-layer collagen-hydroxyapatite scaffold Follow-up: 2 years	A statistically significant improvement in all clinical scores was obtained at 1 year, and a further improvement was found at 2 years. At 2-years, the IKDC subjective score had increased from 48.4±17.8 preoperatively to 82.3±12.2, the IKDC objective evaluation from 40% to 85% of normal knees, and the Tegner score from 2.4±1.7 to 4.5±1.6. The MRI evaluations showed good	Same study with longer follow-up included in table 2.

		defect filling and implant integration but also inhomogeneous regenerated tissue and subchondral bone changes in most patients at both follow-up times. No correlation between the MOCART score and clinical outcome was found.	
Filardo G, Di Martino A et al (2012). Midterm results of a combined biological and mechanical approach for the treatment of a complex knee lesion. Cartilage (3).			full paper not available
Filardo G, Kon E et al (2013). Osteochondral scaffold reconstruction for complex knee lesions: a comparative evaluation. Knee. 20 (6):570-6.	Case series (retrospective comparative study) n=33 patients with complex lesions of the knee Implantation of a biomemtic scaffold (n=33 versus 23 implantation of a matrix assisted autologous chondrocyte transplantation in 2 stages (cell based Hyalograft scaffold) Follow-up: 2 years	IKDC subjective score improved significantly from preoperative score 40.4±14.1 to 69.6±17.0 at 12 months follow-up with a further improvement to 75.5±15.0 (p=0.038) at 24 months follow-up. The same trend was confirmed by VAS and Tegner scores. At final follow-up, the osteochondral scaffold group presented a better subjective IKDC score with respect to the group treated with the chondral scaffold (p=0.034).	Larger and longer follow-up studies included in table 2.
Lee YH, Suzer F and Thermann H (2014). Autologous Matrix-Induced Chondrogenesis in the Knee: A Review. Cartilage 5 (3) 145-153.	Review 10 studies (219 patients) AMIC for knee chondral defects.	The improvements in Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee Subjective, Lysholm and Tegner scores at 2 years were comparable to the published results from autologous chondrocyte implantation (ACI) and matrix ACI techniques for cartilage repair. Our systematic review of the current state of the AMIC technique suggests that it is a promising 1-stage cartilage repair technique. The short-term clinical outcomes and magnetic resonance imaging results are comparable to other cell-based methods. Further studies with AMIC in	Review

		randomized studies versus other repair techniques such as ACI are needed.	

Piontek T, Ciemniewska-Gorzela, K et al (2012). All-arthroscopic AMIC procedure for repair of cartilage defects of the knee. Knee Surgery, Sports Traumatology.	The paper describes all-arthroscopic technique to repair knee cartilage defects using the AMIC technique, which includes the use of a collagen matrix (porcine collagen type I and III) and fibrin glue-technique.		Technical note
Pascarella A, Ciatti R et al (2010). Treatment of articular cartilage lesions of the knee using a modified AMIC technique. Knee Surgery, Sports, Traumatology, Arthroscopy 18: 509-13.	Case series n=19 patients with grade III/IV chondral lesions. 9% osteochondral lesions. Modified AMIC technique with perforations rather than microfractures (Pridie technique) and lesion covered with ChondrGide enriched with bone marrow blood drawn from the knee itself and fixed with fibrin glue. Follow-up: 24 months.	Results according to IKDC, Lysholm Knee Scale revised for chondral injuries, Ikeuchi score and MRI evidence, suggest a good to excellent outcome for the majority of the patients.	Modified AMIC technique enriched with bone marrow blood.
Patrascu JM, Freymann U et al (2010). Repair of a post-traumatic cartilage defect with a cell-free polymer-based cartilage implant: a follow-up at two years by MRI and histological review. Journal of Bone & Joint Surgery - British Volume 92 (8) 1160-1163.	Case report n=1 patient with a post-traumatic chondral defect of the medial femoral condyle managed by microfracture covered with Chondrotissue. Follow-up: 2 years	2 years after the operation patient remained free of pain with full knee function. In every sub category, the Knee Injury and Osteoarthritis Outcome score was 100.	Larger and longer follow-up studies included in table 2.
Siclari A, Mascaro G et al (2014). A 5-year follow-up after cartilage repair in the knee using a platelet-rich plasma-immersed polymer-based implant. The open orthopaedics journal 8 346-354.	Case series n= 52 patients with focal chondral defects treated with subchondral drilling and resorbable polymer-based implants (polyglycolic acid - hyaluronan (PGA-HA) implant (Chondrotissue)) immersed with autologous platelet-rich plasma (PRP). Follow-up: 5 years.	At 5-year follow-up, the KOOS showed clinically meaningful and significant ($p < 0.05$) improvement in all subcategories compared to baseline. Subgroup analysis showed that there were no differences in the clinical outcome regarding defect size and localisation as well as degenerative condition of the knee. Cartilage repair was complete in 20 out of 21 patients at 4-year follow-up as shown by magnetic resonance observation of cartilage repair tissue (MOCART) scoring.	AMIC plus technique.
Schiavone PA, CerciielloS et al (2011).	Case series	At an average FU of 36 months, mean IKDC score	Conference abstract.

The management of knee cartilage defects with modified amic technique: preliminary results. International Journal of Immunopathology & Pharmacology 24 (1:Suppl 2) Suppl-149-52	n=17 ChondroGide Follow-up: 36 months	and Lysholm score improved from 32 to 82 and from 38 to 74. 13 patients out of 17 (76.5%) were satisfied or extremely satisfied with their functional result. MRI control showed reduction of the defect area and subchondral oedema in 10 cases (58.8%). AMIC technique is a relatively new option in the treatment of full thickness cartilage lesions.	
Stelzeneder D, Shetty AA et al (2013). Repair tissue quality after arthroscopic autologous collagen-induced chondrogenesis (ACIC) assessed via T2* mapping. Skeletal Radiology 42 (12) 1657-1664.	Retrospective case series n=10 patients with symptomatic chondral defects in the knee who were treated arthroscopically with microdrilling and atelocollagen/fibrin-gel application (single-stage approach). All defects were ICRS grade III or IV and the sizes were 2-8 cm(2) intra-operatively. Follow-up: 1 year	The mean MOCART score at 1-year follow-up was 71.7 +/- 21.0 ranging from 25 to 95. The mean T2* relaxation times were 30.6 +/- 11.3 ms and 28.8 +/- 6.8 ms for the repair tissue and surrounding native cartilage, respectively. The T2* ratio between the repair tissue and native cartilage was 105% +/- 30%, indicating repair tissue properties similar to native cartilage.	An arthroscopic single-stage procedure using microdrilling in combination with atelocollagen gel and fibrin-glue. Arthroscopic autologous collagen-induced chondrogenesis (ACIC) Not matrix included chondrogenesis.
Shetty AA, Kim SJ et al (2013). Autologous collagen-induced chondrogenesis: single-stage arthroscopic cartilage repair technique. Orthopedics 36 (5) e648-e652.	Retrospective case series n=10 patients with symptomatic chondral defects in the knee who were treated arthroscopically with microdrilling and atelocollagen/fibrin-gel application under carbon dioxide insufflation(single-stage approach). All defects were ICRS grade III or IV and the sizes were 2-8 cm(2) intra-operatively. (Atelocollagen mixed with fibrinogen and thrombin in a 2-way syringe). Follow-up: 2 years.	Mean MOCART score at 1-year follow-up was 70.4 +/- 20.2 (range, 15-95). The MOCART score for patellar lesions was similar to that of lesions in other locations: 73.3 +/- 11.7 vs 68.1 +/- 25.5, respectively. This technique had encouraging clinical results at 2-year follow-up. Morphological MRI shows good cartilage defect filling, and the biochemical MRI suggests hyaline-like repair tissue.	An arthroscopic single-stage procedure using microdrilling in combination with atelocollagen gel and fibrin-glue. Arthroscopic autologous collagen-induced chondrogenesis (ACIC) Not matrix included chondrogenesis.
Shetty AA, Kim SJ et al (2014). Autologous bone-marrow mesenchymal cell induced chondrogenesis: Single-stage arthroscopic cartilage repair. Tissue Engineering and	Case series (prospective) n=30 patients with symptomatic ICRS grade III/IV chondral defects, ranging from 2-9 cm. Surgical procedure involved debridement of	At 2 year follow-up, Lysholm score was 80.1, as compared to 50.8 pre-operatively ($p < 0.05$). KOOS (symptomatic) was 92.1, as compared to 65.7 pre-operatively. IKDC (subjective) was 83, up from 39 preoperatively. The	An arthroscopic single-stage procedure using microdrilling in combination with atelocollagen gel and fibrin-glue. Arthroscopic autologous collagen-

Regenerative Medicine.11 (3) 247-253.	the lesion, microfracture and application of concentrated BMAC with HA and fibrin gel under CO₂ insufflation. Follow-up: 2 years.	mean T2relaxation-times for the repair tissue and native cartilage were 29.1 and 29.9 respectively. Average MOCART score for all lesions was 72. Our technique shows encouraging clinical results at 2 year follow-up. Clinical outcome scores show significant benefit. The morphological MRI shows good cartilage defect filling and the biochemical MRI (T2-mapping) suggests hyaline like repair tissue.	induced chondrogenesis (ACIC) Not matrix included chondrogenesis.
Stanish WD, McCormack R et al (2013). Novel scaffold-based BST-CarGel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial. The Journal of Bone and Joint Surgery 95:1640-5 0.	RCT n=80 patients with a single symptomatic focal lesion on the femoral condyles (BST CarGel =microfracture 41 versus 39 microfracture alone) Follow-up: 12 months	Blinded MRI analysis demonstrated that, at 12 months, when compared with microfracture treatment alone, BST-CarGel treatment met both primary end points by achieving statistical superiority for greater lesion filling (p=0.011) and more hyaline cartilage-like T2 values (p=0.033). The lesion filling values were 92.8%±2.0% for the BST-CarGel treatment group and 85.2%±2.1% for the microfracture treatment group, and the mean T2 values were 70.5±4.5 ms for the BST-CarGel treatment group and 85.0±4.9 ms for the microfracture treatment group. Western Ontario and McMaster Universities Osteoarthritis Index subscales for pain, stiffness, and function yielded equivalent improvement for both groups at 12 months, ($p < 0.0001$). Treatment safety profiles were considered comparable. At 12 months, BST-CarGel treatment resulted in greater lesion filling and superior repair tissue quality compared with microfracture treatment alone. Clinical benefit was equivalent between groups at 12 months, and safety was similar.	BST CarGel a chitosan based biomaterial, mixed with autologous whole blood and applied to a microfractured lesion in which it stabilizes the clot and enhances marrow derived repair. Out of scope as not AMIC.
Shive MS, Hoemann CD, et al (2006). In situ chondroinduction for	Case series n=33	Study showed improved WOMAC scores for pain, stiffness and function.	BST CarGel a chitosan based biomaterial, mixed

cartilage repair. Oper Tech Otthop 16:271-278.	BST-CarGel treatment		with autologous whole blood and applied to a microfractured lesion in which it stabilizes the clot and enhances marrow derived repair. Out of scope as not AMIC.
Mattihas R et al (2014). Arthroscopic treatment of cartilage lesions with microfracture and BST-CarGel. Arthroscopy Techniques. 3 (3), e399-e402.			Describes surgical technique.
Siclari A, Mascaro G et al (2012). A cell-free scaffold-based cartilage repair provides improved function hyaline-like repair at one year. Clinical Orthopaedics & Related Research 470 (3) 910-919.	Case series n=52 patients with cartilage defects Implantation of the polyglycolic acid (PGA)-hyaluronan scaffold with platelet-rich-plasma (PRP) in knee pre-treated with drilling Follow-up: 1 year.	The KOOS sub scores improved for pain (55 to 91), symptoms (57 to 88), activities of daily living (69 to 86), sports and recreation (36 to 70), and quality of life (38 to 73). The histologic evaluation showed a homogeneous hyaline-like cartilage repair tissue. The cell-free PGA-hyaluronan scaffold combined with PRP leads to cartilage repair and improved patient-reported outcomes (KOOS) during 12 months of follow-up. Histologic sections showed morphologic features of hyaline-like repair tissue. Long-term follow-up is needed to determine if the cartilage repair tissue is durable.	AMIC plus technique.
Vannini F et al (2012). 'One step' treatment of juvenile osteochondritis dissecans in the knee: clinical results and T2 mapping characterisation. Orthop Clin N Am 43:237-244.	Case series n=6 Osteochondral repair of knee with BMDC transplantation using a 1 step procedure. Hylofast was used for cell support.	No intraoperative or postoperative complications noted. IKDC showed improvement from 61.0 to 96.5 at follow-up of 3 years. ($p<0.0005$). All patients satisfied with the treatment.	AMIC combined with BMAC.
Wylie JD, Hartley MK et al (2015). What is the effect of matrices on cartilage repair? A systematic review. [Review]. Clinical Orthopaedics & Related Research 473 (5) 1673-1682.	systematic review on articular chondrocyte transplantation or matrix-assisted articular chondrocyte transplantation 2004-14	Articular chondrocyte transplantation shows better patient-reported outcomes at 5 years in patients without chronic symptoms preoperatively compared with microfracture ($p=0.026$). Matrix-assisted articular chondrocyte transplantation consistently showed improved patient-	Systematic review of ACI and MACI

		reported functional outcomes compared with microfracture (p values ranging from < 0.001 to 0.029). Hyalograft C and Chondro-Gide are the matrices with the most published evidence in the literature, but no studies comparing different matrices met our inclusion criteria, because the literature consists only of uncontrolled case series.	

Appendix B: Related NICE guidance for microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

Guidance	Recommendations
Interventional procedures	**Mosaicplasty for knee cartilage defects. NICE interventional procedure guidance 162 ([2006])** 1.1 Current evidence suggests that there are no major safety concerns associated with mosaicplasty for knee cartilage defects. There is some evidence of short-term efficacy, but data on long-term efficacy are inadequate. In view of the uncertainties about the efficacy of the procedure, it should not be used without special arrangements for consent and audit or research. 1.2 Clinicians wishing to undertake mosaicplasty for knee cartilage defects should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's efficacy and the options for alternative treatments. They should provide them with clear written information. In addition, use of the Institute's information for the public is recommended. • Audit and review clinical outcomes of all patients having mosaicplasty for knee cartilage defects. The Institute may review the procedure upon publication of further evidence. **Partial replacement of the meniscus of the knee using a biodegradable scaffold. NICE interventional procedure guidance 430 ([2012])** 1.1 Current evidence on partial replacement of the meniscus of the knee using a biodegradable scaffold raises no major safety concerns. Evidence for any advantage of the procedure over standard surgery, for symptom relief in the short term, or for any reduction in further operations in the long term, is limited in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake partial replacement of the meniscus of the knee using a biodegradable scaffold should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand that there are uncertainties about any possible long-term advantage over other surgical options and that considerable rehabilitation is required after

	this procedure. Clinicians should provide patients with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having partial replacement of the meniscus of the knee using a biodegradable scaffold (see section 3.1). 1.3 The procedure should only be carried out by surgeons who are highly experienced in arthroscopic meniscal surgery. 1.4 NICE encourages further research and data collection on partial replacement of the meniscus of the knee using a biodegradable scaffold. This should include clear descriptions of patient selection and adjunctive treatments. Outcome measures should include symptom relief and functional ability in the short term and the need for further treatment in the longer term. **Arthroscopic radiofrequency chondroplasty for discrete chondral defects of the knee. NICE interventional procedure guidance 493 ([2014])** 1.1 Evidence on the efficacy of arthroscopic radiofrequency chondroplasty for discrete chondral defects of the knee is limited but shows benefit in the short term, and there are no major safety concerns. Therefore this procedure may be used with normal arrangements for clinical governance, consent and audit. 1.2 The procedure should only be carried out by clinicians with specific training in the use of arthroscopic radiofrequency ablation and with particular attention to the avoidance of thermal injury. 1.3 Further research into arthroscopic radiofrequency chondroplasty of the knee should clearly document patient selection and the types of chondral defects being treated. More evidence on long-term outcomes would be useful.
Technology appraisals	**The use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints. NICE technology appraisal 89 ([2005])** 1.1 Autologous chondrocyte implantation (ACI) is not recommended for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up. Patients should be fully informed of the uncertainties about the long-term effectiveness and the potential adverse effects of this procedure. **Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)). [Not yet published].** **Preliminary recommendations** 1.1 Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the

	knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation.

Appendix C: Literature search for microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	30/10/2015	Issue 10 of 12, October 2015
HTA database (Cochrane)	30/10/2015	Issue 3 of 4, July 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	30/10/2015	Issue 9 of 12, September 2015
MEDLINE (Ovid)	29/10/2015	1946 to October Week 4 2015
MEDLINE In-Process (Ovid)	29/10/2015	October 28, 2015
EMBASE (Ovid)	29/10/2015	1974 to 2015 Week 43
PubMed	30/10/2015	n/a
BLIC (British Library)	30/10/2015	n/a

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

Database: Ovid MEDLINE(R) <1946 to October Week 4 2015>
Search Strategy:
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1 Cartilage, Articular/
2 cartilage diseases/
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*)).ti,ab.
4 or/1-3
5 (knee* or patella* or menisc* or genu*).ti,ab.
6 4 and 5
7 knee injuries/
8 or/6-7
9 "prostheses and implants"/
10 tissue scaffolds/
11 9 and 10
12 guided tissue regeneration/

13 ((cartilag*or artific* or synthet* or arthroscop* or chondrocyte* or collagen) 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*)).ti,ab.
14 (AMIC or autologous matrix* induc* chondrogenesis*).ti,ab.
15 (autologous* adj4 cell adj4 implant*).ti,ab.
16 or/11-15
17 16 and 5
18 8 and 17
19 (chondrotissue or chondro-tissue).ti,ab.
20 (chondro-gide or chondro gide).ti,ab.
21 MaioRegen Biojoint* System*.ti,ab.
22 or/19-21
23 18 or 22
24 animals/ not humans/
25 23 not 24