

***Matrix-induced
autologous
chondrocyte
implantation and
autologous
chondrocyte
implantation***

December 2010

MSAC application 1140

Assessment report

© Commonwealth of Australia 2011

ISBN (Print) 978-1-74241-400-0

ISBN (Online) 978-1-74241-401-0

ISSN (Print) 1443-7120

ISSN (Online) 1443-7139

First printed

Paper-based publications

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by MSAC with the assistance of Mr Luis Zamora, Dr Prema Thavaneswaran, Ms Karen Humphreys, and Dr Alun Cameron from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) and Dr Stephen Goodall from the Centre for Health Economics Research and Evaluation (CHERE).

Publication approval number: D0210

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Acronyms and abbreviations

ACI	autologous chondrocyte implantation
ACI-C	autologous chondrocyte implantation-collagen
ACI-P	autologous chondrocyte implantation-periosteum
AE	adverse event
AHMAC	Australian Health Ministers Advisory Council
AMZ	anteromedialization
ANOVA	Analysis of Variance
AOC	autologous osteochondral cylinder
AR-DRG	Australian Refined Diagnosis Related Group
ARTG	Australian Register of Therapeutic Goods
BMI	body mass index
CCI	characterised chondrocyte implantation
CI	95% confidence interval
DOHA	Department of Health and Ageing
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
EMSN	Extended Medicare Safety Net
EQ-5D	EuroQuol Group 5-Dimension Self Report Questionnaire
GRE	gradient-recalled-echo
HCS	heterogeneous compound symmetry
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
KOOS	knee injury and osteoarthritis outcome
LKSS	Lysholm Knee Scoring Scale

LOCF	last observation carried forward
MACI	matrix-induced chondrocyte implantation
MBS	Medicare Benefits Schedule
MOCART	magnetic resonance observation of cartilage repair tissue
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
MST	marrow stimulation technique
MT	magnetisation transfer
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
OATS	osteochondral autologous transplantation
OCD	osteochondritis dissecans
PDI	Pain Disability Index
QALY	quality-adjusted life years
RCT	randomised controlled trial
SD	standard deviation
SF-36	Short Form 36
SPSS	Statistical Package for Social Sciences
TGA	Therapeutic Goods Administration
VAS	visual analog scale

Executive summary

The procedure

Autologous chondrocyte implantation (ACI) is a technique that involves the cultivation of chondrocytes *in vitro*, utilising a two-stage operative approach that is usually spread over approximately five weeks. The aim of this procedure is to replace damaged cartilage with true hyaline cartilage. The first step of this process comprises the arthroscopic removal of healthy articular cartilage from a non-load-bearing region of the knee. Propagation involves isolation of the excised cartilage from the matrix through mincing of the tissue and enzymatic digestion. At this stage the cells may be cryopreserved, prior to *in vitro* cultivation in a monolayer culture, until sufficient numbers of chondrocytes are available for implantation. The process occurs in a medium consisting of growth factors, the patient's own serum, antibiotics, and antifungal agents. The isolated chondrocytes, due to their unstable nature, dedifferentiate in the monolayer culture system which is then reformed into the chondrocytic phenotype with their own newly-produced matrix. The exact manner of chondrocyte culture can vary between different centres.

The second phase of the procedure involves the insertion of the chondrocytes into the defect. Firstly the defect is prepared by excising all damaged cartilage, to the depth of the subchondral bone. The chondrocytes can be inserted into the damaged cartilage in one of two ways. In ACI, the chondrocytes are injected underneath a periosteal (ACI-P) or collagen (ACI-C) flap which is glued to the surrounding cartilage using a fibrin adhesive. An alternative approach termed matrix-induced autologous chondrocyte implantation (MACI) involves seeding chondrocyte cells into a membrane consisting of either porcine type I/type III collagen bilayer, or a synthetic material. The MACI membrane can then be adhered directly to the base of a prepared chondral defect with fibrin glue without an osteal cover. In certain centres, cells are adhered directly to the injured site using fibrin glue, although this is not common.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures — Surgery was engaged to conduct a systematic review of the literature and an economic evaluation on the use of matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation for articular cartilage defects. An Advisory Panel with expertise in this area then evaluated the evidence presented and provided advice to MSAC on the safety, effectiveness and cost-effectiveness of the use of matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation for articular cartilage defects.

MSAC's assessment of matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation

Clinical need

The procedure is targeted towards patients with symptomatic full thickness chondral or osteochondral defects which are surrounded by healthy, normal cartilage in an otherwise healthy knee. ACI is also a viable treatment for cartilage defects in joints other than the knee, including the hip, shoulder, elbow and talus; however, based on the published literature, it appears that after the knee, the ankle is the most common joint treated with ACI.

Prevalence and incidence rates for hyaline cartilage damage in knee joints are unclear, in part because these defects occur as a result of a wide range of injuries. Such defects may occur indirectly as a result of another knee injury, and occur several months or years after that initial injury.

There are some reports which suggest that isolated cartilage damage is quite uncommon, occurring in only eight patients in a series of over 1,000 arthroscopies. However, significant cartilage injury, as assessed by microscopic appearances of cartilage over areas of 'bone bruising' or bony contusion seen on magnetic resonance imaging (MRI), appears to be fairly common. Further, there is data to suggest that cartilage damage may often go undiagnosed, particularly as conventional MRI scans are not as sensitive as arthroscopy for detecting such defects.

Knee injuries that require surgical treatment are associated with a significant impact on quality of life. In particular, patients suffering from such injuries display significantly impaired quality of life in terms of physical functioning, role limitations due to physical problems, pain and social functioning, compared with the general population. Additionally, for individuals who have physically demanding jobs, cartilage injuries can lead to a loss of employment, further impairing their overall quality of life.

Safety

A total of 53 studies were identified for inclusion in the assessment of the safety of MACI and ACI. These included 10 comparative studies, four comparative studies that were treated as case series, and 39 case series. Comparative studies compared MACI or ACI to microfracture, mosaicplasty or debridement.

Overall, safety data was not reported as comprehensively as effectiveness outcomes were in the included comparative studies, with few studies reporting statistical comparisons between MACI/ACI and comparator procedures. This may represent study bias where the primary concern of the authors was to present data on effectiveness, rather than safety.

For the majority of adverse events reported, there were no obvious differences in incidence rates between the MACI/ACI and comparator procedure groups. However one study reported that the incidence of joint swelling and joint crepitation was significantly higher following ACI compared with microfracture. Similarly, the incidence rates for joint effusion and tissue hypertrophy (both symptomatic and asymptomatic) appeared higher following MACI/ACI than comparator procedures. Procedure failure rate was the most commonly reported adverse event, and demonstrated an incidence rate

of 9.5 per cent in the MACI/ACI population, and 11.9 per cent in the comparator procedure population. Major adverse events such as joint infection and deep vein thrombosis were rare in both the MACI/ACI and comparator groups, and there were no reported deaths as a result of the procedures in either group.

Overall, the safety of MACI/ACI appears to be comparable to those comparator procedures evaluated in this assessment.

Effectiveness

A total of 14 comparative studies were identified and included to inform on the effectiveness of MACI and ACI:

- a total of five randomised controlled trials that directly compared MACI or ACI to microfracture or mosaicplasty
- one pseudo-randomised controlled trial that directly compared ACI to mosaicplasty
- eight non-randomised comparative studies that directly compared MACI or ACI to microfracture, mosaicplasty or debridement.

The studies available for this assessment were heterogeneous in terms of the patients recruited, the MACI/ACI technique used and the measures used to assess patient outcomes, which made it difficult to draw direct comparisons between the different procedures across studies. A further limitation of the studies included in this assessment was the length of follow-up reported. It has been suggested that any differences in outcome based on formation of articular rather than fibrocartilage in the defect may be quite subtle and may only reveal themselves after many years of follow-up (five-10 years). However the majority of studies in this assessment reported short to medium-term (one-three years) follow-up of patients.

The most commonly reported functional outcome measures were the Lysholm and Tegner scores. Of the eight studies that reported Lysholm scores, six reported no significant difference in the effectiveness of MACI/ACI over time compared with comparator procedures; however, one study each reported that MACI/ACI was more effective over time compared with microfracture and mosaicplasty. Similarly, of the five studies that reported Tegner scores, four studies reported no significant difference in the effectiveness of MACI/ACI over time compared with comparator procedures; however, one study reported that MACI was more effective over time compared with microfracture.

Most studies that assessed these functional outcomes reported that quality of life and pain scores were not significantly different following MACI/ACI compared with comparator procedures; however, one study did report that the improvement in pain scores following ACI was significantly better compared with debridement.

Imaging outcomes reported in a limited number of studies revealed no significant difference in the quality of articular cartilage repair following MACI/ACI compared with comparator procedures. Similarly, one study reported that at five year follow-up, there was no significant difference in the frequency of radiographic changes that were

indicative of osteoarthritis in MACI/ACI patients compared with patients who underwent microfracture.

Overall, in the short to medium term, the effectiveness of MACI/ACI appears to be comparable to those comparator procedures evaluated in this assessment.

Economic evaluation

There was insufficient evidence to support the superior effectiveness of MACI/ACI for hyaline cartilage damage in knee joints. Therefore a costing analysis of MACI/ACI relative to mosaicplasty and microfracture was undertaken.

The estimated costs of MACI/ACI, mosaicplasty and microfracture were taken from a number of sources. These included the Medicare Benefits Schedule (MBS), Australian Refined Diagnostic Related Group (AR-DRG) cost, prosthesis list and the median charged MBS fee. The model assumes that rehabilitation requirements following these procedures are identical. Consequently, assessment costs and rehabilitation costs have not been considered during the cost analysis.

The total estimated cost of performing the MACI/ACI (biopsy and grafting) procedure is \$14,083 per knee. The comparative costs associated with mosaicplasty and microfracture are \$2,639 and \$1,405, respectively. The incremental cost of MACI/ACI as opposed to mosaicplasty is \$11,444 and \$12,678 for microfracture.

The main difference between the cost of the MACI/ACI, mosaicplasty and microfracture procedures is the cost of the chondrocyte cell culture (\$11,400) and Tisseel sealant (\$380). There are also costs associated with the additional biopsy procedure required during MACI/ACI; however, these are offset somewhat by the mosaicplasty surgical kit.

Based on current MBS utilisation data, it was estimated that approximately 1,000 patients undergo hyaline knee cartilage repair per annum. The estimate total cost of providing 1,000 MACI/ACI procedures per year would be \$14,082,746 per annum, compared to \$1,405,012 for the equivalent number of microfracture procedures. Therefore if MACI/ACI was used instead of microfracture for all 1000 patients, the incremental cost would be \$12,677,734 per annum. Of this an estimated \$365,123 would be attributed to the MBS, representing an additional cost that is not borne when using microfracture. These estimates assume a 100 per cent uptake rate of MACI/ACI.

A sensitivity analysis was performed in order to calculate the potential unmet demand. It was assumed that 11 per cent of patients that undergo knee arthroscopy have cartilage defects and are consequently eligible for MACI/ACI. The number of knee procedures (other than replacement and recapping) performed in private hospitals in Australia in 2008-09 was 64,237 (based on AR-DRG I18Z 2008-09). Therefore if 11 per cent of these patients are suitable for a cartilage repair procedure, potentially 7,066 MACI/ACI procedures could be performed per year.

Based on these data, the estimated total cost of providing 7066 MACI/ACI procedures would be approximately \$99.51 million per annum. The equivalent total cost of microfracture would be approximately \$9.93 million. Therefore if MACI/ACI was used instead of microfracture for all 7,066 patients the incremental total cost would be over \$89.58 million. Of this, \$83.24 million would be required for consumables (mainly the

chondrocyte culture procedure) and the estimated additional cost to the MBS would be \$2.58 million.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of matrix-induced autologous chondrocyte implantation (MACI) and autologous chondrocyte implantation (ACI), which is a therapeutic technology for articular cartilage defects. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's Terms of Reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation for the treatment of articular cartilage defects.

Background

Articular cartilage damage

Cartilage may be classified into three separate types: elastic cartilage, fibrocartilage and hyaline cartilage. These cartilage types differ from each other in their main components, which are produced by chondrocytes (collagen, proteoglycans and elastin). Hyaline cartilage is found in the articular surfaces of bones as well as on the ventral ends of ribs, larynx, trachea and bronchi. In joints, hyaline cartilage covers articular surfaces and plays an important role in decreasing friction and mechanical load on synovial joints, including the knee (Wasiak et al 2007). Hyaline cartilage gives diarthrodial joints excellent load-bearing and wear characteristics, as well as a low coefficient of friction (Bruce et al 2005). It is a tough, semi-transparent, elastic and flexible tissue consisting of cartilage cells (chondrocytes and chondroblasts) scattered through a glycoprotein material and strengthened by collagen fibres. The cartilage cellular matrix is also composed of proteoglycans, noncollagenous proteins, lipids, phospholipids and water (Bruce et al 2005). Articular cartilage has no blood or nerve supply.

Chondral injuries are those in which the hyaline cartilage is damaged. Injuries in which there is damage to both the hyaline cartilage and underlying bone are known as osteochondral injuries. Damage to hyaline cartilage can bring about secondary events such as pain and swelling of the joint, which are caused by the release of shredded cartilage fragments into the synovium. However, patients do not always experience pain because articular cartilage is both aneural and avascular. It is hypothesised that the presence of pain is a result of the increased load on subchondral bone resulting from damage or loss of overlying cartilage (Macmull et al 2010). This can lead to decreased mobility and pain on movement. In some circumstances, deformity and constant pain can result (Wasiak et al 2007).

Osteoarthritis and rheumatoid arthritis are examples of chronic conditions of cartilage damage. Acute damage can also occur to cartilage. Osteochondritis dissecans (OCD) is a disorder in which a fragment of articular cartilage, together with avascular subchondral bone, becomes either partly or completely separated from a joint surface (Marlovits et al 2004). Along with trauma-related damage (mostly resulting from sporting injuries), OCD is a major cause of damage to knee hyaline cartilage. Previous hyaline cartilage damage has been reported to predispose individuals to osteoarthritis, possibly due to the limited capacity of hyaline cartilage to repair itself (Clar et al 2005). In instances of advanced cartilage degeneration or damage the need for knee replacement surgery may arise.

According to expert clinical advice, the severity of articular cartilage damage may be classified into four grades:

- grade I: the cartilage has a soft spot or blisters
- grade II: superficial fissuring of the cartilage surface, velvet-like appearance
- grade III: deep fissuring reaching subchondral bone, including partially detached chondral flaps or crab meat like appearance
- grade IV: erosion to exposed bone.

Matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation

ACI is a technique that involves the cultivation of chondrocytes *in vitro*, utilising a two-stage operative approach that is usually spread over approximately five weeks. The aim of this procedure is to replace damaged cartilage with true hyaline cartilage. The first step of this process involves the arthroscopic removal of healthy articular cartilage from a non-load-bearing region of the knee (Ruano-Ravina and Jato Diaz, 2005). Propagation involves isolation of the excised cartilage from the matrix through mincing of the tissue and enzymatic digestion. At this stage, the cells may be cryopreserved prior to *in vitro* cultivation in a monolayer culture, until sufficient numbers of chondrocytes are available for implantation. The process occurs in a medium consisting of growth factors, the patient's own serum (to 10 per cent final volume), antibiotics (such as gentamicin sulfate), and antifungal agents (such as amphotericin). The isolated chondrocytes, due to their unstable nature, dedifferentiate in a monolayer culture system, which is then reformed into the chondrocytic phenotype with their own newly-produced matrix (Brittberg, 1999). The exact manner of chondrocyte culture can vary between different centres.

The second phase of the procedure involves the insertion of the chondrocytes into the defect. Firstly, the defect is prepared by excising all damaged cartilage to the depth of the subchondral bone. The chondrocytes can be inserted into the damaged cartilage in one of two ways. In ACI, the chondrocytes are injected underneath a periosteal (ACI-P) or collagen (ACI-C) flap which is glued to the surrounding cartilage using a fibrin adhesive. An alternative approach termed MACI involves seeding chondrocyte cells into a membrane consisting of either a porcine type I/type III collagen bilayer (Bartlett et al 2005), or a synthetic material. The MACI membrane can then be adhered directly to the base of a prepared chondral defect with fibrin glue without an osteal cover. Certain centres adhere cells directly to the injured site using fibrin glue, although this is not common.

Depending on the depth of the damage to the articular joint, bone grafting may be necessary. If the osteochondral defect depth is less than approximately 8 mm, bone grafting is not necessary; however, if the lesion is deep enough to have affected the subchondral endplate, concomitant or staged bone grafting may be preferred (Bruce et al 2005). MRI or arthroscopy is used to identify whether or not the subchondral bone is damaged. If bone grafting is performed, a three to four month healing period is recommended prior to the implantation of chondrocytes. However, a newer method termed the 'sandwich technique' has been used to perform simultaneous bone grafting and cartilage implantation. Using this technique, whether or not bone grafting is performed, the cultured chondrocytes are injected under this periosteal flap which is sealed peripherally with a biological fibrin glue (Ruano-Ravina and Jato Diaz, 2005). However, for the purpose of this review, bone grafting was considered a separate procedure.

When performing surgical procedures to repair articular cartilage, where required it is important that an attempt is made to improve patellofemoral mechanics. None of the chondroplasty procedures are common, and as they are operations requiring anaesthesia and a sterile environment, would be performed in an operating theatre in a private or public hospital.

ACI is also a viable treatment for cartilage defects in joints other than the knee, including the hip, shoulder, elbow and talus (Bradley and Petrie 2001; Johansen et al 2000; Koulalis et al 2002; Romeo et al 2002). However, based on the published literature, it appears that after the knee, the ankle is the most common joint treated with ACI.

When performing either MACI/ACI, microfracture, debridement or mosaicplasty for cartilage repair, recovery will take at least 12 months. The clinical expert opinion of the Advisory Panel suggests that rehabilitation is similar for each of these techniques, and is likely to vary more between individual surgeons than the techniques themselves.

Intended purpose

Suitability for the MACI/ACI technique is determined through arthroscopic evaluation of the location, depth and size of the lesion, as well as the quality of the surrounding cartilage, degree of undermining cartilage and the status of the opposing chondral surface (Brittberg 2008). Ideally, the procedure is targeted towards patients with symptomatic full-thickness chondral or osteochondral defects which are surrounded by healthy, normal cartilage in an otherwise healthy knee (Brittberg 2008). In defects less than 2 cm², the technique should ideally be used as a second line treatment option after bone stimulation techniques have failed (Brittberg 2008). In larger defects, the technique may be used as a first line option. The technique is not indicated in patients with severe osteoarthritis, rheumatoid arthritis or active autoimmune connective tissue diseases, or in patients with concomitant malignancies (Brittberg 2008).

Clinical need/burden of disease

Prevalence and incidence rates for hyaline cartilage damage in knee joints are unclear, in part because these defects occur as a result of a wide range of injuries (Jobanputra et al 2001). Such defects may occur indirectly as a result of another knee injury, and occur several months or years after that initial injury.

There are some reports which suggest that isolated cartilage damage is quite uncommon, occurring in only eight patients in a series of over 1,000 arthroscopies (Hopkinson et al 1985). However, significant cartilage injury, as assessed by microscopic appearances of cartilage over areas of 'bone bruising' or bony contusion seen on MRI, appears to be fairly common. Further, there is data to suggest that cartilage damage may often go undiagnosed, particularly as conventional MRI scans are not as sensitive as arthroscopy for detecting such defects (Jobanputra et al 2001).

Knee injuries that require surgical treatment are associated with a significant impact on quality of life. In particular, patients suffering from such injuries display significantly impaired quality of life in terms of physical functioning, role limitations due to physical problems, pain and social functioning, compared with the general population (Jobanputra et al 2001). Additionally, for individuals who have physically demanding jobs, cartilage injuries can lead to a loss of employment, further impairing their overall quality of life.

Existing procedures

There are various surgical and non-surgical options currently available for the treatment of articular cartilage defects. These include marrow stimulation techniques (eg

microfracture), autologous grafting procedures (eg osteochondral autologous transplantation (OATS) and mosaicplasty), and autologous chondrocyte transplantation techniques (eg MACI/ACI).

According to Bruce et al (2005), there is currently no gold standard treatment for articular cartilage injuries. A number of factors impact upon treatment choice, including lesion size, physiologic age, desired activity level, job status, compliance capabilities, and associated pathologies (Bruce et al 2005). First-line treatment for nondisplaced OCD lesions in young patients with open physes involves nonsurgical palliative treatment. This may include weight-bearing with crutches or braces, maintenance of knee range of motion, quadriceps strengthening and judicious use of nonsteroidal anti-inflammatory medications. In addition, intra-articular viscosupplementation injections have demonstrated possible efficacy in symptom relief in the osteoarthritic knee. Steroidal injection into the joint can also be used to help alleviate symptoms.

A diverse range of surgical procedures has been developed to treat articular cartilage defects of the knee, which have predominantly been aimed at relief of symptoms and improvement in functionality (Ruano-Ravina and Jato Diaz, 2005). Ruano-Ravina and Jato Diaz (2005) state that these techniques can be divided into four categories (Table 1): symptomatic treatment, stimulation of bone marrow-derived cells, chondrogenesis within transplanted tissue/cells, and transplantation of osteochondral plugs.

Table 1 Methods used in the surgical management of articular cartilage defects

Symptomatic treatment	Lavage Debridement
Stimulation of bone marrow-derived cells	Bridie drilling Microfracturing Superficial abrasion Deep abrasion or spongification
Chondrogenesis of tissue cells	Periosteal grafting Perichondral grafting Autologous chondrocyte implantation
Transplantation of osteochondral plugs	Allografting Autografting/mosaicplasty/osteochondral autologous transplantation

Table adapted from Ruano-Ravina and Jato Diaz (2005)

In many cases, symptomatic treatment is initially sought. Lavage and debridement are the two most common forms of surgical symptomatic treatment. The removal of collagen fragments from the cartilage and synovium can reduce inflammation in the joint for a period of time, but cannot cure the defect. However, a randomised controlled trial (RCT) by Moseley and colleagues (2002) found no differences in outcomes between a lavage group, a lavage and debridement group and a control group, indicating no significant benefit in these techniques. During the lavage procedure, inflammatory mediators are removed, whereas during debridement the removal of loose or free chondral/osteochondral fragments in the knee is performed (Bruce et al 2005). Unfortunately, neither lavage nor debridement provide adequate treatment for active patients, as neither procedure addresses the defect in the cartilage and subchondral bone.

Marrow-stimulating techniques such as drilling, microfracture and abrasion arthroplasty involve perforating the subchondral bone in a controlled fashion in order to stimulate the mitogenesis of mesenchymal stem cells to the site of injury (Bruce et al 2005). These methods have led to mixed results, and may result in fibrocartilage composed of Type 1

collagen (rather than the more durable hyaline cartilage) due to healing. Additionally, the long-term outcomes of marrow-stimulating techniques remain unclear despite some good short-term outcomes.

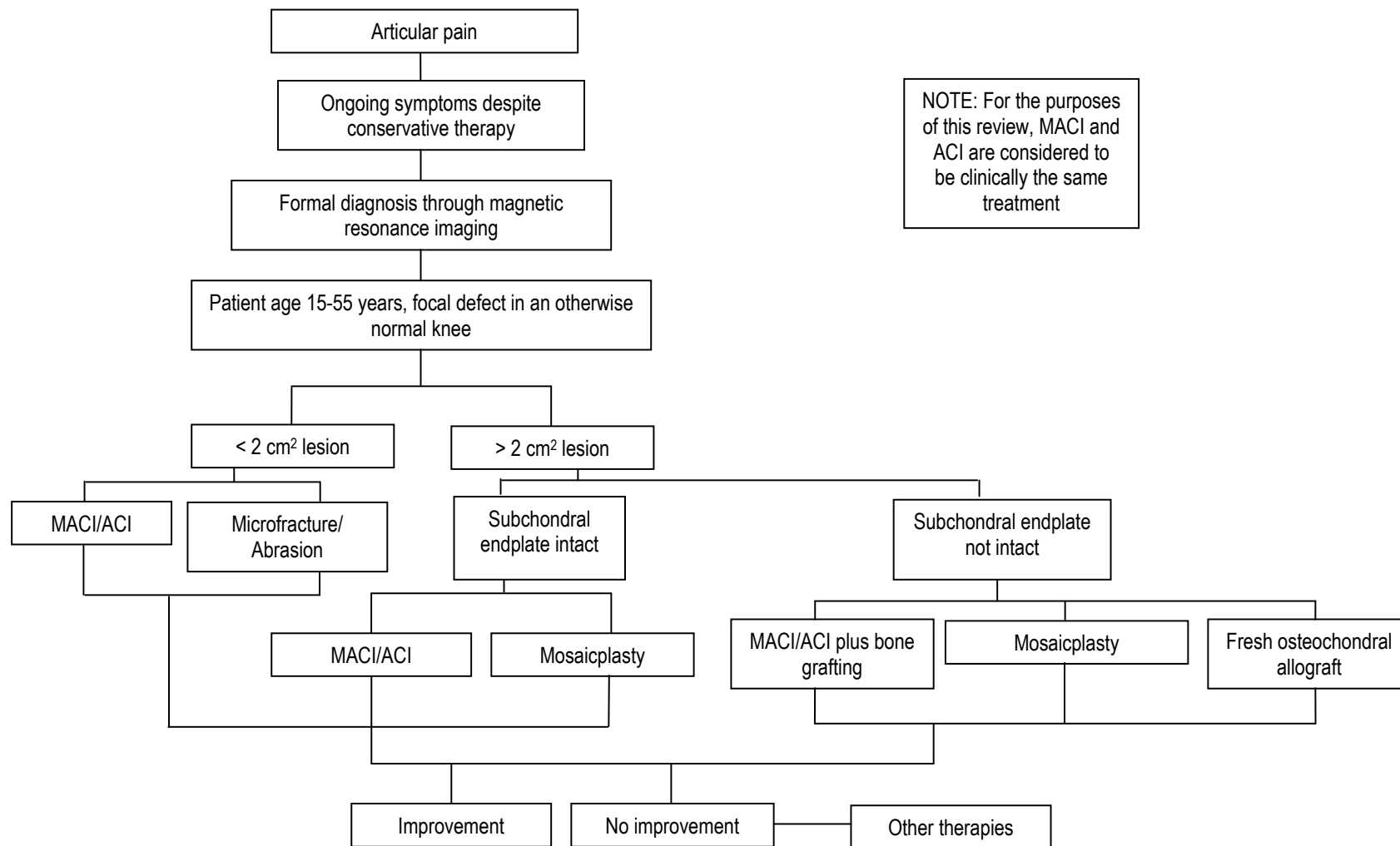
Bruce et al (2005) classifies osteochondral transfer and ACI as secondary procedures. Osteochondral transfer, also known as mosaicplasty, can be performed using either autologous tissue or cadaveric allograft tissue. Holes bored into the cartilage and bone of the damaged area are filled with cartilage and bone plugs removed from healthy, non-weight-bearing areas of the joint. This technique differs from ACI in that 'plugs' are used to supplement the osteochondral lesions, with no cultivation of cartilage cells or use of a flap. Mosaicplasty can have deleterious effects which do not occur with microfracture or MACI/ACI. Both of the techniques used in mosaicplasty hold risks, including donor-site morbidity in osteochondral allografting and possible disease transmission, unavailability of size-matched donor grafts, sterile effusion and poor bony incorporation in autografting. Consequently, some level of immunologic rejection occurs at the bony level, which may affect long-term outcomes (Bruce et al 2005).

Comparator

Expert clinical advice suggests that there are a number of alternative procedures which could be chosen according to clinical presentation, each of which are outlined in the clinical decision-making pathway (Figure 1). The comparator procedures for MACI/ACI are:

- mosaicplasty
- microfracture
- conservative treatments
- fresh osteochondral allograft.

Figure 1 Clinical decision-making pathway



Marketing status of the technology

According to the Applicant, there are three different sources of MACI/ACI in Australia:

- Genzyme market MACI[®], which is Therapeutic Goods Administration (TGA) approved.
- Device Technologies (Orthogen) market ACI (Arthromatrix Cartilage Implantation), which is TGA approved.
- Mercy Tissue Engineering market Cartogen. Although the company is licensed by the TGA, no approval for Cartogen could be identified.

Table 2 lists the devices related to this application listed on the Australian Register of Therapeutic Goods (ARTG) database. TISSEEL has recently been approved by the TGA for the following: 'TISSEEL is indicated as a sealant and/or adhesive for use in autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte implantation (MACI) procedures'.

Table 2 Devices related to this application on the ARTG

ARTG number	Product	Sponsor
81929	TISSEEL DUO 500 two component fibrin sealant syringe	Baxter Healthcare Pty Ltd
147141	TISSEEL VH S/D (frozen) fibrin sealant syringe	Baxter Healthcare Pty Ltd
157704	TISSEEL VH/SD	Baxter Healthcare Pty Ltd
121056	Matricel ACI-MAIX Collagen Membrane - Tissue reconstructive material, biological	Verigen Australia Pty Ltd

ARTG: Australian Register of Therapeutic Goods

Current reimbursement arrangement

Current MBS item numbers for procedures relating to hyaline cartilage damage are presented in Table 3. Prior to July 2006 item numbers 49563 and 49557 were used for MACI/ACI procedures, as clinicians considered that the benefits for these items adequately reflected the time and expertise required for these procedures. Although neither item was intended to cover MACI/ACI, item 49563 covered the osteochondral graft and item 49557 covered the biopsy requirement of the ACI procedure, even though this item was originally introduced for diagnostic purposes.

Table 3 Current MBS item numbers for procedures related to hyaline cartilage damage

MBS item number	Descriptor	Fee	Number of claims (July 2005 to June 2006)	Number of claims (July 2008 to June 2009)
49500	KNEE, arthrotomy of, involving one or more of; capsular release, biopsy or lavage, or removal of loose body or foreign body	Fee: \$355.90 Benefit: 75% = \$266.95	698	1,012
41512	MEATOPLASTY involving removal of cartilage or bone or both cartilage and bone, not being a service to which item 41515 applies	Fee: \$533.80 Benefit: 75% = \$415.35	308	350
49561	KNEE, ARTHROSCOPIC SURGERY OF, involving one or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes associated debridement, osteoplasty or chondroplasty - not associated with any other arthroscopic procedure of the knee region	Fee: \$637.05 Benefit: 75% = \$477.80	37,393	45,541
49558	KNEE, arthroscopic surgery of, involving one or more of: debridement, osteoplasty or chondroplasty - not associated with any other arthroscopic procedure of the knee region	Fee: \$257.95 Benefit: 75% = \$193.50	2,041	1,643
49559	KNEE, arthroscopic surgery of, involving chondroplasty requiring multiple drilling or carbon fibre (or similar) implant; including any associated debridement or osteoplasty - not associated with any other arthroscopic procedure of the knee region	Fee: \$386.30 Benefit: 75% = \$289.75	194	196
49562	KNEE, ARTHROSCOPIC SURGERY OF, involving one or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes chondroplasty requiring multiple drilling or carbon fibre (or similar) implant and associated debridement or osteoplasty - not associated with any other arthroscopic procedure of the knee region	Fee: \$695.15 Benefit: 75% = \$521.40	2,588	3,245
49563 ^a	KNEE, arthroscopic surgery of, involving one or more of: meniscus repair; osteochondral graft; or chondral graft - not associated with any other arthroscopic procedure of the knee region	Fee: \$752.95 Benefit: 75% = \$564.75	1,007	934
49557 ^a	KNEE, diagnostic arthroscopy of (including biopsy, simple trimming of meniscal margin or plica) - not being a service associated with any other arthroscopic procedure of the knee region	Fee: \$257.95 Benefit: 75% = \$193.50	1,865	1,381
49518	KNEE, total replacement arthroplasty of	Fee: \$1245.50 Benefit: 75% = \$934.15	11,965	15,763
49503	KNEE, partial or total meniscectomy of, repair of collateral or cruciate ligament, patellectomy of, chondroplasty of, osteoplasty of, patellofemoral stabilisation or single transfer of ligament or tendon (not being a service to which another item in this Group applies) - any one procedure	Fee: \$462.65 Benefit: 75% = \$347.00	358	294
49506	KNEE, partial or total meniscectomy of, repair of collateral or cruciate ligament, patellectomy of, chondroplasty of, osteoplasty of, patellofemoral stabilisation or single transfer of ligament or tendon (not being a service to which another item in this Group applies) - any two or more procedures	Fee: \$694.05 Benefit: 75% = \$520.55	512	413

MBS: Medicare Benefits Schedule; a: Prior to July 2006 this MBS item number was used for matrix-induced autologous chondrocyte implantation/autologous chondrocyte implantation procedures by clinicians

Approach to assessment

Objective

To determine whether there is sufficient safety, effectiveness and cost-effectiveness evidence to have MACI/ACI listed on the MBS for the treatment of articular cartilage defects.

Review of literature

Literature sources and search strategies

The medical literature was systematically searched to identify relevant studies and reviews on the safety, effectiveness and cost-effectiveness of using MACI/ACI for the treatment of articular cartilage defects. The literature was searched from the inception of the electronic databases to March 2010. Appendix C describes the search terms and electronic databases that were used for this search and other sources of evidence that were investigated.

Inclusion/exclusion criteria

Detailed inclusion and exclusion criteria applied to the identified citations for assessing the safety and effectiveness of MACI/ACI are detailed in Appendix C.

PICO (population, intervention, comparator, and outcome) criteria were developed with guidance from the Advisory Panel to assist in specifying the search strategy (Table 4).

Table 4 PICO criteria

Population	Intervention	Comparator	Outcomes
<p>Patients aged between 15 and 55 years suffering from a focal defect in an otherwise normal knee.</p> <p>Populations with damage to other locations (eg shoulder, ankle) were reported separately.</p>	<p>Autologous chondrocyte implantation</p> <p>Matrix-induced autologous chondrocyte implantation</p>	<p>Mosaicplasty</p> <p>Microfracture</p> <p>Conservative treatments</p> <p>Fresh osteochondral allograft</p>	<p><i>Effectiveness</i></p> <p>Key functional and imaging outcomes, including:</p> <p>Quality of life scores</p> <p>6-minute walking times</p> <p>Time of rehabilitation</p> <p>Pain</p> <p>Development of arthritis</p> <p>Imaging evaluation (arthroscopy, magnetic resonance imaging)</p> <p>Knee function (Modified Cincinnati knee score)</p> <p>Re-treatment, including requirement for knee replacements.</p> <p>Expert clinical opinion suggested that due to recovery, final outcomes should be reported at 12 months or later.</p> <p><i>Safety</i></p> <p>All adverse events were recorded.</p>
<p>Clinical questions</p> <ul style="list-style-type: none"> • Is autologous chondrocyte implantation as safe as, or safer than, mosaicplasty? • Is autologous chondrocyte implantation as effective as, or more effective than, mosaicplasty? • Is autologous chondrocyte implantation as cost-effective as, or more cost-effective than, mosaicplasty? • Is matrix-induced autologous chondrocyte implantation as safe as, or safer than, mosaicplasty? • Is matrix-induced autologous chondrocyte implantation as effective as, or more effective than, mosaicplasty? • Is matrix-induced autologous chondrocyte implantation as cost-effective as, or more cost-effective than, mosaicplasty? • Are there any specific subgroups of patients for which autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation is more or less safe, effective or cost-effective? • Are there any technical specifications of autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation which are more or less safe or effective? • Are there any long-term safety or effectiveness implications associated with the use of autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation? • Is autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation reversible when complications are seen? 			

The following statements provide further detail regarding the clinical questions outlined above:

Target population

- Patients with osteoarthritis and rheumatoid arthritis were excluded. Patients with trauma and OCD were included.
- Populations were grouped according to the location of the defect. Patients with knee injuries were the primary population. Patients with defects in other areas (such as ankle or shoulder) were reported separately where possible.

- MACI/ACI is recommended for the treatment of lesions that are greater than or equal to 2 cm²; however, the clinical expert opinion of the Advisory Panel suggested that in clinical practice, decisions regarding the use of this procedure are not always made based on lesion size. Therefore, in this review, a broader scope was taken and all relevant studies, including those that did not use these strict criteria, were included in order to reflect the variability in clinical practice.
- Outcomes were not separated according to location of injury within a specific joint.
- The depth of the defect was not essential to the assessment, as all damaged cartilage should be removed to the depth of the subchondral bone. If the subchondral endplate has been damaged, a bone graft must be undertaken prior to chondrocyte implantation. Patients with bone damage were not excluded.
- Due to disease progression MACI/ACI should not be indicated for patients older than 55 years.

Intervention

- MACI and ACI were considered clinically similar techniques that could be pooled. Hence, the assessment considered the intervention of chondrocyte cell-based products. Where the data allowed, similar techniques were presented together (eg in the case of similar flaps for ACI, or similar matrices (synthetic versus biological) for MACI).
- Differences between the techniques of cell culture are commercial-in-confidence, and therefore were not be a consideration for this assessment.
- ‘Hybrid’ studies (eg where ACI and mosaicplasty were used together) were excluded, as the relative effectiveness of one technique over the other was unclear.
- All fibrin glues (bovine or human) have similar modes of action and none is considered superior over the others.
- Stem cell implantation was excluded.
- The osteochondral sandwich technique is a different procedure and was not considered as part of this assessment.
- MACI/ACI technologies include:
 - CondroCelect/TGX001 (TiGenix)
 - BioCart II (ProChon Biotech)
 - CARTIPATCH (TBF Genie Tissulaire)
 - INSTRUCT (CellCoTec BV)
 - Genzyme (MACI)
 - Merci (ACI).

Comparator

- All comparators listed in Table 4 were included. Expert clinical advice suggested that there are many appropriate alternatives to MACI/ACI and the decision to use one procedure over another is based on clinician experience.

Outcomes

- Patient-related outcomes were considered to be superior to imaging outcomes. Using both types of outcomes accounted for discrepancies in the alternative. It was acknowledged that patient feedback can be subjective, and that technical measures may not always relate to patient issues.
- Due to the recovery time for the procedure, only outcomes assessed at a minimum of 12 months after implantation were included.
- Most studies grouped outcomes in terms of good/excellent and fair/poor. Using this summary it was appropriate to combine outcome scores from a variety of measures in order to pool data across studies.

Outcomes during the first 12 months were reported to take into account potential decrements in quality of life during patient recovery and rehabilitation.

Data extraction and analysis

Data were extracted by one researcher and checked by a second using standardised data extraction tables developed a priori. Data were only reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. If no data were reported for a particular outcome then no value was tabulated. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies, including numerator and denominator information.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2009).

These dimensions (Table 5) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 5 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The <i>P</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 8

Strength of the evidence

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (Table 6).

Table 6 Designations of levels of interventional evidence (NHMRC 2009)

Level	Intervention ^a
I ^b	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial ^c Cohort study Case-control study Interrupted time series with a control group
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study ^d Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

^aA systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence

^bDefinitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b)

^cThis also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C)

^dComparing single arm studies i.e. case series from two studies

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence

Quality

The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (NHMRC 2000). This checklist was used for trials and cohort studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the United Kingdom National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al 2001).

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and *P*-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000).

Size of effect

For intervention studies, it was important to assess whether statistically significant differences between the comparators were also clinically important. Where possible, the size of the effect was determined, as well as whether the 95% confidence interval (CI) included only clinically important effects.

Relevance of evidence in individual studies

The outcomes being measured in this report should be appropriate and clinically relevant. Clinical input from the Advisory Panel was provided to ensure that inadequately validated (predictive) surrogate measures of a clinically relevant outcome were avoided wherever possible (NHMRC 2000).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted as suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2009). Five components are considered essential by the NHMRC when judging the body of evidence:

- the evidence base — this includes the number of studies sorted by their methodological quality and relevance to patients
- the consistency of the study results — whether the better quality studies had results of a similar magnitude and in the same direction (ie homogenous or heterogenous findings)
- the potential clinical impact — appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test
- the generalisability of the evidence to the target population
- the applicability of the evidence — integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 7) (NHMRC 2009).

Table 7 Body of evidence assessment matrix

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias, or a systematic review or multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population	Population/s studied in the body of evidence are similar to the target population	Population/s studied in body of evidence different from target population for guideline, but it is clinically sensible to apply this evidence to target population	Population/s studied in body of evidence different from target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: NHMRC (2009)

Expert advice

An Advisory Panel with expertise in orthopaedics, rheumatology and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Descriptive characteristics of included studies

The systematic literature search identified 361 potentially relevant articles, of which 248 were retrieved for more detailed evaluation. Retrieved studies included systematic reviews and primary studies. In total, 181 retrieved articles were excluded (Appendix J).

A total of 67 studies, including 10 systematic reviews, five randomised controlled trials (RCTs), one pseudo-randomised trial, 12 non-randomised comparative studies (four treated as case series for the purposes of safety assessment), and 39 case series were eligible for appraisal and inclusion in this assessment (Appendix E).

Studies for assessment of safety

Fifty three studies were identified for inclusion in the assessment of the safety of MACI and ACI. This included 10 comparative studies, four comparative studies that were treated as case series, and 39 case series. Comparative studies compared MACI or ACI with microfracture, mosaicplasty or debridement. Sample sizes ranged from 10 to 309 patients, with safety data reported for an overall total of 3,254 patients.

Studies for assessment of effectiveness

A total of 14 comparative studies were identified and included to inform on the effectiveness of MACI and ACI. These studies allowed the assessment of the comparative effectiveness of the procedures within this review.

The systematic literature search revealed:

- a total of five RCTs that directly compared MACI or ACI to microfracture (Basad et al 2010; Knutsen et al 2004; Saris et al 2008) or mosaicplasty (Bentley et al 2003; Dozin et al 2005)
- one pseudo-RCT that directly compared ACI to mosaicplasty (Horas et al 2003)
- eight non-randomised comparative studies that directly compared MACI or ACI to microfracture (Kon et al 2008; Trattnig et al 2008; Welsch et al 2008a; Welsch et al 2008b; Welsch et al 2009), mosaicplasty (Derrett et al 2005; Salzman et al 2009) or debridement (Fu et al 2005).

A subsequent section will examine these studies in greater detail and appraise their methodological quality.

Of these 14 comparative studies, four studies (401 patients) reported that they were sponsored by, or had at least one author who was affiliated with, a commercial entity, while nine studies (359 patients) reported no such conflicts of interest. One study (60 patients) failed to report the source of funding.

Duplication of results

It is unlikely that significant duplication of the results has occurred across this dataset. There were various cases where the same patient population (or part of patient population) was used in multiple reports. In some cases, different outcomes were reported in those different reports. In cases where the same outcome was reported in more than one report, the most recent data was used for analysis.

Systematic reviews and health technology assessments

A list of electronic databases and websites of international health technology assessment (HTA) agencies searched can be found in Appendix C. A total of three health technology assessments were identified (Clar et al 2005; Jobanputra et al 2001; Kunzl et al 2009).

An additional seven systematic reviews were also identified through the literature search (Brittberg 2010; Kon et al 2009; Magnussen et al 2008; Ruano-Ravina and Jato Diaz 2005; Vasiliadis et al 2010; Wasiak et al 2007; Zengerink et al 2010).

MACI/ACI for cartilage defects of the knee

Study description

Nine systematic reviews, including three health technology assessments (HTAs), examined the use of ACI for treating cartilage defects of the knee, compared with alternative treatments.

The three HTAs (Jobanputra et al 2001; Clar et al 2005; and Kunzl et al 2009) investigated the clinical outcomes following ACI, with two also examining the economic evidence relating to ACI. The reviews by Jobanputra et al (2001) and Kunzl et al (2009) searched multiple databases, with Jobanputra et al (2001) also using other sources (meeting abstracts, broad internet searches, contact with leading researchers). The review by Jobanputra et al (2001) included any published or unpublished report on any patient group, describing the use of ACI and reporting patient outcome data. In the review by Kunzl et al (2009) controlled clinical studies on ACI with more than 20 patients and minimum follow-up of one year were included. In both reviews, two independent reviewers assessed the studies for quality and eligibility. The review by Clar et al (2005) was an update to the HTA by Jobanputra et al (2001). The report added to the evidence base from the previous report and did not repeat the review of the case series included in Jobanputra et al (2001). An update of the search strategy was performed to identify studies published after the previous review. Again, two independent reviewers assessed studies and extracted study data.

The other six systematic reviews also focused on the clinical outcomes of safety and effectiveness following ACI or, more specifically, MACI only. With the exception of the review by Brittberg (2009) all reviews searched multiple databases for relevant studies. The reviews by Kon et al (2009), Ruano-Ravina and Jato Diaz (2005) and Wasiak et al (2007) specified that two or more independent researchers were used to assess studies.

Magnussen et al (2008) included prospective comparative studies with treatment of full-thickness lesions, a minimum of 30 patients, a minimum of one year follow-up and comparison of ACI or mosaicplasty with another treatment method. Ruano-Ravina and Jato Diaz (2005) included systematic reviews, clinical trials, meta-analyses, cohort studies, case control studies and case series with more than 20 patients, that aimed to analyse the safety and/or effectiveness of ACI using suitable outcome measures. Wasiak et al (2007) was a Cochrane review that included randomised or quasi-randomised trials comparing ACI with any other type of treatment (including no treatment or placebo) for symptomatic cartilage defects of the medial or lateral femoral condyle, femoral trochlea or patella. Vasiliadis et al (2010) was an update to the systematic review published by Wasiak et al (2007). Two reviews focussed specifically on the MACI technique. Brittberg (2009) included preclinical and clinical primary MACI studies published in peer-reviewed

journals, reporting use of autologous chondrocytes seeded on the preferred type I/III collagen membrane. Kon et al (2009) included studies which reported clinical outcomes of patients treated with MACI in the knee using various products.

Statistical summaries were generally not undertaken in the reviews, due to small study numbers and clinical and methodological differences between studies.

Efficacy

The HTA by Jobanputra et al (2001) identified 17 ACI studies which met the inclusion criteria, covering at least 2,600 patients. All of these studies were case series studies with variable follow-up periods. The authors stated that due to the low quality of the included studies, the efficacy data may be subject to bias, and no definitive conclusions could be drawn. However, the authors state that all but one of the included studies reported improvements in patient status. The update by Clar et al (2005) identified four RCTs (covering 266 patients) as well as new case series (covering 101 patients). Of the RCTs, one found that ACI gave superior results to mosaicplasty, while another concluded that there is little difference between the two techniques at two years. Similarly, comparison of ACI with microfracture in one study resulted in little differences between the techniques at two years. Another study compared MACI with microfracture, but did not have sufficient follow-up results to identify any differences in treatment effect.

The HTA by Kunzl et al (2009) included nine comparative studies (seven RCTs and two non-randomised comparative studies) and six systematic reviews covering 566 patients. The studies compared ACI with microfracture and mosaicplasty, as well as with other forms of ACI. The results from this HTA were consistent with the findings of earlier systematic reviews, which show that there is no evidence that ACI is superior to other treatment alternatives in the treatment of osteochondral defects.

The other systematic reviews, like the HTAs, reported generally inconclusive findings on the efficacy of ACI. The systematic review by Magnussen et al (2008) included five RCTs and one prospective non-randomised comparative study reporting on 421 patients. Of the included studies, one used MACI and three used ACI (with either a periosteal or collagen cover) and compared them with alternative techniques such as microfracture or mosaicplasty. Another study compared ACI with MACI, while another compared microfracture and mosaicplasty. The overall results demonstrated that no technique consistently resulted in superior outcomes compared with the others. When compared to the preoperative assessment, all treatment techniques resulted in improved clinical outcome measures regardless of the technique used.

Ruano-Ravina and Jato Diaz (2005) included four systematic reviews, three RCTs, six case series, and two cost analyses. The RCTs, which compared ACI with microfracture, transplantation of osteochondral cylinders and mosaicplasty, did not show clear superiority of ACI in comparison to these techniques. Additionally, while the case series suggested positive results, they lacked quality. The systematic reviews suggested that ACI should remain an experimental therapy until more evidence is available. The authors of the review concluded that there is no evidence that ACI is superior to conventional techniques.

Wasiak et al (2007) included four studies which compared ACI to other cartilage repair methods. The authors noted that the studies were generally small and with little power to detect useful clinical differences between groups. Two studies compared ACI with

mosaicplasty. One found no significant differences in terms of functional assessments, while the other noted significantly better outcomes for mosaicplasty in only one of three functional assessment scoring systems used. One study compared ACI to microfracture and found little difference between the two techniques in terms of functional assessment and arthroscopic evaluation. The rate of failure was also similar between groups. Another study compared MACI with microfracture and reported mixed results, some of which favoured MACI, but did not contain enough long-term results to reach definitive conclusions. The authors concluded that there was insufficient evidence to determine whether ACI is superior to either mosaicplasty or microfracture in the treatment of full thickness defects of the knee. In an update, Vasiliadis et al (2010) included nine studies covering 626 patients, including four studies previously reported on by Wasiak et al (2007). The studies demonstrated that ACI was associated with improvements in clinical outcomes when compared to baseline; however, the results did not suggest a clear superiority of ACI when compared other treatment strategies. As in the earlier review, the authors concluded that there is insufficient evidence to determine whether ACI is superior to other techniques.

Two reviews focussed specifically on the effectiveness of the MACI technique. Brittberg (2009) included one prospective RCT and 11 studies case series or case reports which reported on the use of MACI. The RCT compared MACI with collagen-covered ACI. Data from both the RCT and case series demonstrated improvements in clinical outcomes following MACI; however, due to the low quality and small sample of most of the included studies, interpretation of the data was limited. Despite this, the authors concluded that MACI is a promising technique for treating symptomatic full-thickness defects. The other review by Kon et al (2009) included 18 studies on MACI reporting on 731 patients, including two RCTs, three prospective comparative studies, 11 prospective cohort or case series studies and two retrospective case series. The authors stated that a significant improvement in clinical outcomes following MACI was observed across all the studies, suggesting that MACI is a promising technique for the treatment of symptomatic full-thickness defects. However, the average quality level of the included studies was low, and comparison with other techniques was not undertaken in the review.

Safety

The HTAs by Jobanputra et al (2001) and Clar et al (2005) noted the adverse events reported for individual studies, but made no overall conclusions. Kunzl et al (2009) identified that the most frequently reported side effects in the included studies for microfracture, mosaicplasty, ACI and MACI were joint swelling, joint crepitation, arthralgia and graft hypertrophy. The need for surgical revision was commonly reported for ACI, MACI and microfracture. Due to inconsistent reporting, overall conclusions regarding the comparative safety of the various techniques were not possible.

In the review by Magnussen et al (2008), complications were reported by all of the included studies, with arthrofibrosis, superficial wound infection and tissue hypertrophy the most commonly-reported complications. Generally the frequency of these complications was low. Ruano-Ravina and Jato Diaz (2005) concluded that in terms of safety the data suggested that ACI does not pose any additional threats to the patient.

Wasiak et al (2007) noted that the included studies reported intraoperative or postoperative complications associated with arthrotomy of the knee, such as calf-vein thrombosis requiring anticoagulation and superficial infection, along with a number of

common minor complications. The authors highlighted that major adverse events following ACI are rare, and were not observed in the studies included in the review. Vasiliadis et al (2010) found that complication rates between ACI and other treatment techniques were comparable, with the exception of graft hypertrophies which were increased following the ACI-P technique.

Of the two reviews focussing specifically on MACI, Brittberg (2009) stated that postoperative complications/adverse events associated with MACI were rare, and included tissue hypertrophy, infections, subsequent surgical procedures and treatment failure. Among the included studies the incidence rates of postoperative complications ranged from 0 to 6.3 per cent. Graft failures in the knee were also reported at a similar incidence rate ranging from 0 to 6.3 per cent. Kon et al (2009) indentified that complications reported in the 18 studies included hypertrophy, joint stiffness, graft detachment and synovitis. These complications occurred in patients who had undergone MACI with various products. Further complications of hypertrophy, graft detachment and partial ossification were reported by one study using atellocollagen in conjunction with a periosteal flap.

Cost-effectiveness

Two HTAs included an evaluation of the economic evidence relating to ACI. Jobanputra et al (2001) based the economic evaluation on data from two studies. The review estimated that at the time of publication, ACI performed in the United Kingdom would cost £4667 or £8167 for cell culture and surgery, depending on the service provider used for cell culture. Incremental cost over two years when set against comparator treatments was estimated at £3771 or £7271 for cell culture, surgery and rehabilitation. The authors stated that the cost effectiveness analysis was limited by the lack of data available, but suggested that at the time of writing the costs of ACI were substantial compared to other treatments, which had similar outcomes. The updated HTA by Clar et al (2005) attempted to calculate reliable costs per quality-adjusted life-year; however, this was not possible due to the absence of necessary data. The authors suggested that ACI has the potential to be a cost-effective treatment alternative, but this had not yet been demonstrated by the available evidence.

MACI/ACI for cartilage defects of the ankle

The systematic review by Zengerink et al (2010) aimed to summarise all eligible studies to compare the effectiveness of treatment strategies for osteochondral defects of the ankle, specifically the talus. Medline, EMBASE, CENTRAL and DARE were searched from January 1966 – 2006 to identify relevant RCTs or quasi-experimental research (including case series). Treatment strategies included non-operative treatment (rest or cast), excision of the fragment, excision and curettage, excision and curettage and drilling/microfracturing, placement of a cancellous bone graft, antegrade (transmalleolar) drilling, OATS, ACI, retrograde drilling and fixation of the lesion. Extensive inclusion and exclusion criteria were used, with two reviewers assessing each article independently. Fifty two studies were included in the review, of which four described the results of ACI in 59 patients. There were no comparative studies on ACI. Based on the results of four case series, in 45 of 59 patients (76%) a successful result (good or excellent result using one of the various scoring systems available) was reported. For individual studies the success rate varied from 70 – 92 per cent. No safety results were provided in the review, and the authors did not make specific conclusions regarding ACI.

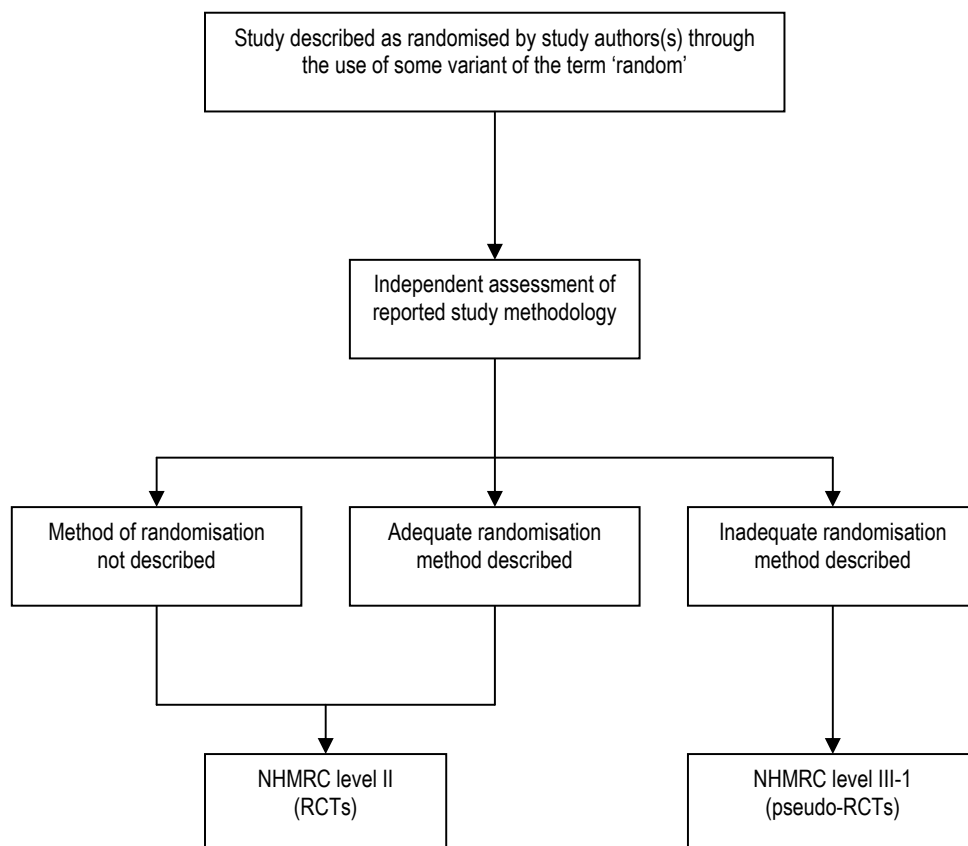
Critical appraisal of randomised controlled studies

Summaries of the quality of the five RCTs and one pseudo-RCT included in this review are reported in Table 19 and Table 20 in Appendix D and briefly described below.

Studies were classified utilising the NHMRC Hierarchy of Evidence (NHMRC 2000) and allocated the classification of level II randomised controlled trial or level III-1 pseudo-randomised controlled trial based on the process outlined in Figure 2. Study quality was assessed according to the methods outlined in Section 6 of the Cochrane Reviewers' Handbook (Higgins and Green 2008) and the CONSORT Statement (Altman et al 2001).

A number of key appraisal parameters are applicable to both RCTs and pseudo-RCTs. Hence, for parameters where differentiation between the study designs is not relevant, these studies have been grouped together to better allow for the description of the higher-level evidence as a whole.

Figure 2 Method of assessing studies for assignment of NHMRC levels of evidence II and III-1



Study design details

Sample size

Across the six studies sample sizes ranged from 40 patients (20 in each study group) to 118 patients (57 in one study group and 61 in the other study group). Only one study had more than 50 patients in each study group (Saris et al 2008).

Participants

Five of the six studies clearly described their eligibility criteria for the recruitment of patients. These five studies described both the inclusion and exclusion criteria, and considered a variety of factors when recruiting patients including age, lesion size and grade, comorbidities and willingness to comply with the rehabilitation protocol. With respect to lesion size, two studies only included patients with a lesion size of greater than 2 cm², while three studies included patients with a lesion size of less than, as well as greater than, 2 cm². One study did not report its inclusion criteria with regard to lesion size.

Study groups were reported to be generally well-matched at baseline with respect to factors such as age, weight/body mass index (BMI) and lesion size and grade. In the five studies where gender was reported, there were more males than females enrolled. Four studies reported on previous surgical treatments, and study groups were generally well-matched for this outcome at baseline.

Randomisation, concealment and implementation

Of the five studies considered level II evidence, all employed adequate methods of randomisation, including sealed numbered envelopes, computerised random number generators, random number tables or an interactive voice response (IVR) system. Further prevention of selection bias through allocation concealment was not reported in any of the five studies.

In the one study considered level III-1 evidence, patients were assigned to treatment groups using alternate consecutive allocation. This study did not report whether allocation concealment was used.

Blinding

Two of the six studies did not report on blinding status, while one study reported that patients were not blinded to the treatment assignment. The three remaining studies specifically reported employing some form of blinding of outcome assessors, including blinding pathologists and scientists analysing histological sections and radiologists analysing postoperative radiographs.

Interventions and outcomes

Interventions were generally clearly detailed and the majority of studies defined primary outcomes. The majority of studies utilised commonly used, validated outcome instruments for assessment of patient outcomes.

Results reporting and analyses

Numbers analysed

Four studies did not report undertaking power calculations; however, one of these studies did acknowledge that the small number of patients was a limitation of their study. The two remaining studies reported undertaking power calculations on appropriate

outcomes and recruiting the sample size necessary to detect statistically meaningful differences between the two groups.

Five studies did not report whether they undertook an intention-to-treat or per-protocol analysis. One study reported that whenever possible, comparisons between the two study groups were based on the intention-to-treat principle, that is, all randomised eligible patients were included and considered in the arm assigned at randomisation, regardless of compliance to the assigned treatment (Dozin et al 2005).

Statistical methods

The analysis techniques employed were consistently reported, with five of the six studies explicitly listing the statistical tests employed. Four studies prospectively identified an alpha level for statistical significance, most frequently of 0.05.

Outcomes and estimation

The included studies were thorough in reporting the results of each primary outcome defined. The mean was the most frequently employed indicator of central tendency, with almost all studies including some measure of estimation; standard deviations, 95% CI and ranges were reported where appropriate.

Adverse events were not well reported. While five of the six studies reported safety outcomes, most studies described events only briefly, with a discussion of individual incidents.

Follow-up and losses to follow-up

Follow-up time varied between the six studies, ranging from two to three month postoperative observations to five-year postoperative functional assessment. However, most studies employed a medium-term follow-up period, undertaking follow-up between one and three years after surgery.

Losses to follow-up were reported in all six studies. Three of the six studies reported that no patients were lost to follow-up. Of the remaining studies, one reported losing four patients from an initial study group of 60, another reported losing three patients from an initial study group of 47, while the third study reported losing 33 patients from an initial study group of 118.

Critical appraisal of non-randomised comparative studies

An appraisal of the quality of the eight level III-2 studies included in this review is reported in Appendix H, and briefly summarised below.

Study design details

Participants

Sample sizes across the eight studies ranged from a total of 18 patients (nine in each study group) to 116 patients (58 in each study group). With respect to lesion size, one study only included patients with a lesion size of greater than 2 cm², while four studies included patients with a lesion size of less than, as well as greater than, 2 cm². Three studies did not report their inclusion criteria with regard to lesion size.

Blinding

None of the eight studies reported whether blinding of outcome assessors was undertaken.

Interventions and outcomes

Both the MACI/ACI and comparator interventions were clearly detailed in four studies; primary outcomes were defined well overall, with a clear focus towards clinical outcomes. Five studies briefly reported on safety outcomes, and five studies considered imaging outcomes.

Results reporting and analysis

Statistical methods

The analysis techniques employed were consistently reported, with each of the eight studies explicitly listing the statistical tests employed. All studies also reported a pre-defined alpha level that would be considered statistically significant.

Follow-up and losses to follow-up

The length of the follow-up period was reported in all eight studies, and there was a consistent focus on medium-term follow-up, with the majority of studies undertaking follow-up between one and three years after surgery.

Losses to follow-up were reported in seven studies. Of these, five reported that no patients were lost to follow-up. One study reported losing 17 patients from an initial study group of 73, while another study reported losing 20 patients from an initial study group of 116.

Is it safe?

Summary of safety data from level II and III studies

Included studies

Of the 14 comparative studies included (NHMRC level II and III evidence), 10 studies provided some information on adverse events. The remaining four studies presented no adverse event numerical data or statements; however, this does not necessarily indicate an absence of complications in these studies. Safety outcomes of interest were clinical adverse events and technical adverse events related to MACI/ACI and comparator procedures. The adverse events reported by each study are shown in Table 8. From the safety data, it was possible to calculate incidence rates of the various adverse events. While only one study reported the total number of knees, all studies reported the total number of patients; thus, incidence rates were calculated in terms of number of patients in the study group.

Table 8 Adverse events reported in studies providing level II and III safety evidence

Study	MACI/ACI			Comparator procedure		
	Intervention	No. of patients (knees)	Adverse event (number of events) (resolution of adverse event, where reported)	Intervention	No. of patients (knees)	Adverse event (number of events) (resolution of adverse event, where reported)
Level II studies						
Basad 2010 ^a	MACI (collagen matrix)	40 (...)	Persistent pain after 12 months (1) (retrograde bone grafting performed due to persistent subchondral oedema. This relieved pain)	Microfracture	20 (...)	0
Bentley 2003 ^b	ACI (periosteum or collagen)	58 (...)	NA	Mosaicplasty	42 (...)	NA
Knutsen 2004 & 2007 ^c	ACI (periosteum)	40 (...)	Treatment failure (9) (1 treated with total knee replacement, 7 treated with microfracture, 1 treated with microfracture plus high tibial osteotomy) Symptomatic tissue hypertrophy (10) (arthroscopic debridement) Psoriatic arthritis (1) (...)	Microfracture	40 (...)	Treatment failure (9) (5 treated with repeat microfracture, 2 treated with mosaicplasty, 1 treated with total knee replacement, 1 treated with ACI) Arthrofibrosis (1) (patient required manipulation and operative release) Requirement for debridement (3) (minor debridement)
Saris 2008 & 2009 ^d	ACI (periosteum)	51 (...)	Treatment failure (2) (patients underwent reintervention) Musculoskeletal and connective tissue disorders (39) (...) Arthralgia (24) (...) Cartilage hypertrophy (including asymptomatic) (14) (...) Joint crepitation (9) (...) Joint swelling (7) (...) Joint effusion (5) (...) Chondropathy (3) (...) Synovitis (1) (...) Graft complications (3) (...) Therapeutic product ineffective (4) (...)	Microfracture	61 (...)	Treatment failure (7) (patients underwent reintervention) Musculoskeletal and connective tissue disorders (36) (...) Arthralgia (26) (...) Cartilage hypertrophy (including asymptomatic) (7) (...) Joint crepitation (2) (...) Joint swelling (3) (...) Joint effusion (3) (...) Chondropathy (1) (...) Synovitis (2) (...) Therapeutic product ineffective (9) (...)
Level III-1 studies						
Horas 2003	ACI (periosteum)	20 (...)	Partial treatment failure (1) (...) Occasional joint locking, adhesions (1) (arthroscopy) Anterior cruciate ligament partial rupture (1) (arthroscopy) Extension deficit (1) (arthroscopy and release of adhesions) Knee joint swelling (1) (...) Flexion deficit (1) (...) Passing irritation infrapatellar branch of saphenous nerve (2) (...) Concretion of knee capsule (1) (arthroscopy) Valgus malalignment (1) (arthroscopy) Lateralisation of patella (1) (lateral release) Recurrent knee joint effusion (1) (...) Recurring knee joint effusion plus extension deficit (1) (arthroscopy)	Mosaicplasty	20 (...)	Extension deficit (1) (arthroscopy) Haemarthrosis (2) (arthroscopy) Flexion deficit (2) (...) Multiple joint effusions plus flexion deficit (1) (joint effusions) Superficial wound infection plus flexion deficit (1) (...) Passing irritation sensitive branch of peroneal nerve (1) (...) Occasional joint locking plus adhesions (1) (arthroscopy and release of adhesions) Occasional blockade of knee joint (1) (arthroscopy) Passing irritation infrapatellar branch of saphenous nerve (1) (...) Flexion deficit plus adhesions (1) (arthroscopic release of adhesions)

Table 8 (continued)

Adverse events reported in studies providing level II and III safety evidence

Study	MACI/ACI			Comparator procedure		
	Intervention	No. of patients (knees)	Adverse event (number of events) (resolution of adverse event, where reported)	Intervention	No. of patients (knees)	Adverse event (number of events) (resolution of adverse event, where reported)
Level III-2 studies						
Derrett 2005 ^e	ACI (periosteum or collagen)	53 (...)	Unanticipated arthroscopy (19) (3/19 received unanticipated second arthroscopy) Second ACI (1) (...) Manipulations under anaesthesia (8) (...)	Mosaicplasty	20 (...)	Unanticipated arthroscopy (6) (2/6 received unanticipated second arthroscopy) ACI (1) (...) Manipulation under anaesthesia (1) (...) Knee aspiration (1) (...)
Fu 2005 ^f	ACI (periosteum)	58 (58)	Treatment failure (4) (2 treated with graft removal, 1 treated with total knee replacement, 1 treated with reimplantation) Diagnostic arthroscopy (4) (...) Meniscectomy or meniscal repair (3) (...) Lysis of adhesions (3) (...) Loose body or fragment removal (3) (...) Patellar realignment (2) (...) Debridement of loose or unstable periosteal patch (3) (...) Debridement of graft hypertrophy (2) (...)	Debridement	58 (58)	Treatment failure (3) (1 treated with unicompartmental knee replacement, 1 treated with subsequent abrasion chondroplasty performed on treated defect, 1 treated with osteochondral graft plugs) Not specified subsequent operation (1) (...)
Kon 2008 ^g	MACI (Hyalograft C)	40 (...)	0	Microfracture	40 (...)	Treatment failure (1) (patient was reoperated)
Salzmann 2009 ^h	MACI (collagen matrix)	9 (...)	NA	Mosaicplasty	9 (...)	NA
Welsch 2008 ^a	MACI (Hyalograft C)	10 (...)	NA	Microfracture	10 (...)	NA

ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation; NA: not applicable; :not reported.

^eThe efficacy population (defined as patients who provided data from at least 1 follow-up visit \geq 6 months postoperatively) for the intervention group was 39 and the efficacy population for the comparator group was 17. Basad et al 2010 also reported the following adverse events, however did not specify the treatment group in which they occurred: suspected meniscal tear after 12 months (1) (...), subchondral oedema at 12 months (1) (...); NA = not applicable

^bBentley et al 2003 reported the following adverse events, however did not specify the treatment group in which they occurred: patients slow to mobilise during rehabilitation requiring manipulation under anaesthesia (3) (1 patient required arthroscopy and arthrolysis to mobilise knee), development of calf vein thrombosis at 10 weeks (1) (patient treated with anticoagulants), superficial infection (1) (resolved with antibiotics)

^cFailures defined as the requirement for operation because of symptoms due to a lack of healing of the treated defect. The need for shaving or trimming of the defect was not considered a failure

^dThis study reported that in the ACI group 88% of patients had \geq 1 adverse events, 78% of patients had \geq 1 adverse events related to procedure, 25% of patients had \geq 1 severe adverse events, and 9% of patients had serious adverse events, while in the microfracture group, 82% of patients had \geq 1 adverse events, 62% of patients had \geq 1 adverse events related to procedure, 25% of patients had \geq 1 severe adverse events, and 18% of patients had serious adverse events

^eThe study population of this study includes a subset of patients (in both intervention and comparator groups) from Bentley et al 2003. The number of patients from the Bentley et al 2003 study was not reported. The overall number of unanticipated surgery, inpatient episodes, or outpatient consultations was reported as 26 in the intervention group and 8 in the comparator group, however, the subtotals of adverse events did not total to these reported number

^fPatients in the intervention group were considered to have had experienced treatment failure if they were reimplanted with cultured chondrocytes for the same defect or their ACI grafts delaminated or were completely removed

^gA procedure was defined as a failure if the patient required reoperation because of symptoms due to primary defects

^hSalzmann et al 2009 reported that there was no significant difference between the treatment groups in terms of the presence or absence of subchondral bone marrow oedema, granulation tissue, cysts or joint effusion

ⁱThere is potential patient overlap between patients in this study and patients in Trattinig et al 2008, Welsch et al 2008b and Welsch et al 2009. This study reported that there was no significant difference between intervention and comparator groups in terms of the presence or absence of marrow oedema, granulation tissue or cysts, and joint effusion. Furthermore, delamination, cleft formations and hypertrophy were not observed.

Adverse events

Few included studies reported statistical comparisons between MACI/ACI and comparator procedures in terms of adverse events. This may be due to the rare nature of many of these events. Salzman et al (2009) reported that there was no significant difference between the MACI and mosaicplasty groups in terms of the presence or absence of subchondral bone marrow oedema, granulation tissue, cysts or joint effusion. Similarly, Welsch et al (2008a) reported that there was no significant difference between the MACI and microfracture groups in terms of presence or absence of subchondral bone marrow oedema, granulation tissue, cysts or joint effusion.

Table 9 displays the incidence rates of the various reported adverse events. There were no clear differences between the MACI/ACI and comparator procedure groups for the majority of adverse events reported. Procedure failure rate was the most commonly reported adverse event, and demonstrated an incidence rate of 9.5 per cent in the MACI/ACI population and 11.9 per cent in the comparator procedure population. Following failure of MACI/ACI, patients underwent reimplantation or were treated with a variety of alternative procedures including total knee replacement and microfracture. Fu et al (2005) reported that the rate of treatment failure was not significantly different following ACI or debridement; however, in patients who were not classified as treatment failures but still underwent subsequent operations, more patients in the ACI group underwent subsequent procedures compared with the debridement group ($P<0.001$). Saris et al (2008) reported that the incidence of joint swelling was significantly higher following ACI compared with microfracture ($P=0.022$); however, it was noted that this was observed most frequently in the first 14 days after arthrotomy in the ACI group. Similarly, Saris et al (2008) reported that the incidence of joint crepitation was significantly higher following ACI compared with microfracture ($P=0.028$). Overall, the incidence rates for joint effusion and tissue hypertrophy (both symptomatic and asymptomatic) also appeared higher following MACI/ACI than comparator procedures.

Major morbidities such as infection and deep vein thrombosis were rare in both the MACI/ACI and comparator groups, and there were no reported deaths as a result of any of the procedures in either group.

Table 9 Summary of clinical adverse events in level II and III studies providing safety evidence

Adverse event	MACI/ACI		Comparator procedures	
	Incidence* n/N (%)	No. of studies reporting outcome	Incidence* n/N (%)	No. of studies reporting outcome
Persistent pain after 12 months	1/40 (2.5%)	1
Treatment failure	16/169 (9.5%)	4	19/159 (11.9%)	3
Adhesions	2/20 (10%)	1
Requirement for debridement	3/40 (7.5%)	1
Arthrofibrosis	1/40 (2.5%)	1
Occasional blockade of knee joint	1/20 (5%)	1
Joint locking	1/20 (5%)	1	1/20 (5%)	1
ACL partial rupture	1/20 (5%)	1
Extension deficit	2/20 (10%)	1	1/20 (5%)	1
Haemarthrosis	2/20 (10%)	1
Joint swelling	8/71 (11.3%)	2	3/61 (4.9%)	1
Flexion deficit	1/20 (5%)	1	5/20 (25%)	1
Passing irritation sensitive branch of peroneal nerve	1/20 (5%)	1
Passing irritation infrapatellar branch of saphenous nerve	2/20 (10%)	1	1/20 (5%)	1
Concretion of knee capsule	1/20 (5%)	1
Valgus malalignment	1/20 (5%)	1
Lateralisation of patella	1/20 (5%)	1
Knee joint effusion	7/71 (9.9%)	2	4/81 (4.9%)	2
Superficial wound infection	1/20 (5%)	1
Tissue hypertrophy (symptomatic and asymptomatic)	24/91 (26.4%)	2	7/61 (11.5%)	1
Psoriatic arthritis	1/40 (2.5%)	1
ACI	NA	NA	1/20 (5%)	1
Arthralgia	24/51 (47%)	1	26/61 (42.6%)	1
Not specified subsequent operation	1/58 (1.7%)	1
Knee aspiration	1/20 (5%)	1
Joint crepitation	9/51 (17.6%)	1	2/61 (3.3%)	1
Chondropathy	3/51 (5.9%)	1	1/61 (1.6%)	1
Synovitis	1/51 (1.9%)	1	2/61 (3.3%)	1
Graft complications	3/51 (5.9%)	1
Unanticipated arthroscopy	19/53 (35.8%)	1	6/20 (30%)	1
Second ACI	1/53 (1.9%)	1	NA	NA
Manipulations under anaesthesia	8/53 (15%)	1	1/20 (5%)	1
Diagnostic arthroscopy	4/58 (7.5%)	1
Meniscectomy or meniscal repair	3/58 (5.2%)	1
Lysis of adhesions	3/58 (5.2%)	1
Loose body or fragment removal	3/58 (5.2%)	1
Patellar realignment	2/58 (3.4%)	1
Debridement of loose or unstable periosteal patch	3/58 (5.2%)	1
Debridement of graft hypertrophy	2/58 (3.4%)	1

*Incidence is reported in terms of number of patients

ACI: autologous chondrocyte implantation; ACL: anterior cruciate ligament; MACI: matrix-induced autologous chondrocyte implantation; NA: not applicable; ...: not reported.

Summary of safety data from level IV studies

Included studies

Thirty three level IV studies reported safety data on MACI or ACI procedures. Additionally, three non-randomised comparative studies and one RCT with inappropriate comparisons have been treated as level IV studies and their study arms included for safety data only (Ergelet et al 2009; Ferruzzi et al 2008; Steinwachs et al 2007, Wondrasch et al 2009). Where studies compared different types of procedures (eg ACI-P versus ACI-C) or different surgical approaches (eg open ACI versus arthroscopic ACI), these cohorts were combined. A summary of included studies is displayed in Table 21 (Appendix F). Where reported, follow-up was longer than that reported for the comparative studies and ranged from one month to six years. Studies which did not report safety data were excluded.

Those studies which reported study periods covered the years 1987 to 2006 inclusive. The total number of patients across the studies was 2,410. The mean age across the studies ranged from 15 to 48 years (excluding one study which did not report mean age data). There were more males than females. One of the 37 studies did not specify its follow-up period, and 15 studies did not report losses to follow-up.

Adverse events

The 37 included studies reported intraoperative and/or postoperative adverse events, and these events are detailed in Table 22 (Appendix F). Commonly reported adverse events included treatment failure, need for subsequent surgical procedures, and graft hypertrophy. Following failure of MACI/ACI, patients underwent reimplantation or were treated with a variety of alternative procedures including debridement, microfracture and total knee replacement. There were a total of 1,025 adverse events reported in the studies. Given the fact that these events occurred across 2,410 patients, the incidence of reported adverse events appears relatively high; however, few studies clearly stated whether all adverse events reported were directly related to the MACI/ACI procedure. Additionally, many of the adverse events reported were not serious in nature. Major morbidities such as joint infection and deep vein thrombosis were rare, and there were no reports of any deaths as a result of MACI or ACI procedures.

Is it effective?

Clinical outcomes

Lysholm score

The Lysholm knee score is a condition-specific outcome measure that contains eight domains: limp, locking, pain, stair-climbing, use of supports, instability, swelling, and squatting. An overall score of 0 to 100 points is calculated, with 95 to 100 points indicating an excellent outcome, 84 to 94 points a good outcome, 65 to 83 points a fair outcome; and <65 points a poor outcome.

Eight studies (three RCTs, one pseudo-RCT and four comparative studies) were identified that compared Lysholm scores for patients that underwent MACI/ACI with patients that underwent microfracture (Basad et al 2010; Knutsen et al 2004; Trattnig et al 2008; Welsch et al 2008a; Welsch et al 2009) or mosaicplasty (Dozin et al 2005; Horas et al 2003; Salzmann et al 2009).

Basad et al (2010) reported that the difference between Lysholm patient scores at baseline and 24 month follow-up was significant for MACI and microfracture patients ($P<0.0001$ for both); however, MACI was significantly more effective over time than microfracture ($P=0.005$). Knutsen et al (2004) reported that at two and five year follow-up, Lysholm scores had improved significantly compared with the baseline score in both the ACI ($P<0.003$ and $P<0.05$) and microfracture ($P<0.0001$ and $P<0.05$) groups; however, the two groups did not differ significantly with regard to Lysholm scores at one, two and five year follow-up. The studies by Trattnig et al (2008), Welsch et al (2008a) and Welsch et al (2009) reported that Lysholm scores were not significantly different between the MACI and microfracture groups.

Dozin et al (2005) reported that the number of patients who experienced a complete recovery (as indicated by a Lysholm score of 90-100) in the ACI and mosaicplasty groups was not significantly different. Horas et al (2003) reported that based on the postoperative Lysholm score, the recovery after ACI was slower than after mosaicplasty at six month ($P<0.015$), 12 month ($P<0.001$) and 24 month ($P<0.012$) follow-up. In contrast, Salzmann et al (2009) reported that recovery after ACI, as indicated by the Lysholm score, was faster than after mosaicplasty ($P=0.04$).

Tegner score

The Tegner activity level scale was designed to lend a numeric score to a patient's activity level (0 to 10 points). Zero represents disability secondary to knee problems, one through five represents work or recreational sports ranging from sedentary jobs to heavy manual labour, six through nine represents increasing recreational and competitive sports, and a score of 10 is assigned to national- or international-level soccer.

Five studies (two RCTs, one pseudo-randomised controlled trial and two comparative studies) were identified that compared Tegner scores for patients that underwent MACI/ACI with patients that underwent microfracture (Basad et al 2010; Knutsen et al 2004; Kon et al 2008) or mosaicplasty (Horas et al 2003; Salzmann et al 2009).

Basad et al (2010) reported that the difference in Tegner scores between baseline and two year follow-up for the MACI and microfracture groups was significant ($P < 0.0001$ for both); however, MACI was significantly more effective over time than microfracture ($P = 0.03$). Knutsen et al (2004) reported that at five year follow-up, the mean Tegner score had improved significantly compared with the baseline value in both the ACI ($P = 0.007$) and microfracture ($P = 0.002$) groups; however, there was no significant difference between the two treatment groups. Kon et al (2008) reported that the resumption of sports activity as reflected by the Tegner score was similar in both the MACI and microfracture groups at two year follow-up, and this remained stable in the MACI group at five year follow-up but worsened in the microfracture group.

The study by Horas et al (2003) reported that at two year follow-up, the Tegner activity score was not significantly different between ACI and microfracture groups. Similarly, Salzmann et al (2009) reported that Tegner scores were not significantly different following MACI mosaicplasty.

International Cartilage Repair Society (ICRS) score

The International Cartilage Repair Society (ICRS) scoring scheme was specifically designed to evaluate the quality of repair tissue in patients. This scoring scheme assesses six components of repair in histology sections including matrix, cell distribution, subchondral bone, surface, cartilage mineralisation and cell population viability.

Two RCTs were identified that compared ICRS scores for patients that underwent MACI/ACI with patients that underwent microfracture (Basad et al 2010; Knutsen et al 2004). Basad et al (2010) reported that the difference between ICRS patient scores at baseline and 24 month follow-up was significant for MACI and microfracture patients ($P < 0.0001$ for both); however, MACI was significantly more effective over time than microfracture ($P = 0.03$). Knutsen et al (2004) reported that the scores from the ICRS macroscopic evaluation at the second-look arthroscopy performed two years after the procedure were not significantly different in the ACI and microfracture groups.

Cincinnati knee rating score

The Cincinnati knee rating scale assesses subjective symptoms (eg pain, swelling, giving way) and functional activity level (eg walking, climbing stairs, running and jumping, twisting). Fifty points are assigned to each category, for a total of 100 points.

Two studies (one RCT and one comparative study) were identified that compared Cincinnati scores for patients that underwent MACI/ACI with patients that underwent microfracture (Bentley et al 2003) or mosaicplasty (Salzmann et al 2009). Bentley et al (2003) reported that overall, 88 per cent (51/58) of ACI patients had an excellent or good result compared with 69 per cent (29/42) of mosaicplasty patients; however, this difference was not statistically significant. Similarly, Salzmann et al (2009) reported that Cincinnati scores following MACI (mean 74.3, SD 16.2) were not significantly different compared with scores following mosaicplasty (mean 68.3, SD 18.3).

International Knee Documentation Committee (IKDC) score

The IKDC form is a joint-specific tool for evaluating symptoms, function and sports activity applicable to a variety of knee conditions. The subjective form consists of 18 questions and can be scored when 16 of the 18 questions are answered (90%). The raw scores are summed and transformed to a scale of 0 (worst possible) to 100 (highest possible). A change in score of 11.5 points on the 100-point scale represents an improvement in condition.

One comparative study was identified that compared IKDC scores for patients that underwent MACI with patients that underwent microfracture (Kon et al 2008). This study reported that at five year follow-up, a greater improvement in IKDC objective ($P < 0.001$) and subjective ($P = 0.003$) scores was observed in MACI patients compared with microfracture patients.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The Knee Injury and Osteoarthritis Outcome Score (KOOS) evaluates five dimensions: pain (nine items), symptoms (seven items), activities of daily living (17 items), sport and recreation function (five items), and knee-related quality of life (four items). Each item is graded on a five point Likert scale (0-4). Each subscale is summed and transformed to a score of 0 (worst possible) to 100 (best possible).

One comparative study was identified that compared KOOS for patients that underwent ACI with patients that underwent microfracture (Saris et al 2008). This study reported that the adjusted means for the change from baseline to 12 and 18 month follow-up in overall KOOS and the subdomains for pain, symptoms/stiffness, activities of daily living, and quality of life were not significantly different for ACI and microfracture patients. However, the improvement in overall KOOS from baseline to 36 month follow-up was significantly greater in ACI (mean 21.25, SD 3.6) compared with microfracture patients (mean 15.83, SD 3.48) ($P=0.048$).

Meyers score

The Meyers score evaluates pain, function and range of motion. An excellent score (18 points) is given if the patient has complete relief of pain, no limp and a range of motion of 0 to 130° or more; could perform normal activities; and had returned to work. A good score (15 to 17 points) is given if the patient has returned to work and can perform the activities of daily living, but has occasional pain or swelling, no more than a slight limp, and a range of motion of at least 0 to 90°. A fair score (12 to 15 points) is given if the patient has returned to, but has modified, work-related activities and those of daily living; might have frequent swelling; has less than 90° of motion; and occasionally needs medication for pain. A poor score (less than 12 points) is given if there is little or no improvement in the patient's complaints or functional capacity.

One pseudo-RCT was identified that compared Meyers scores for patients that underwent ACI with patients that underwent mosaicplasty (Horas et al 2003). This study reported that at six month, one year and two year follow-up, the Meyers score was not significantly different in ACI patients compared with mosaicplasty patients.

Quality of life scores

Three studies (one RCT and two comparative studies) were identified that compared pain scores for patients that underwent MACI/ACI with patients that underwent microfracture (Knutsen et al 2004) or mosaicplasty (Derrett et al 2005; Salzmann et al 2009).

The Short Form-36 (SF-36) is a validated, generic quality of life instrument. This 36-item questionnaire measures several dimensions of health, including physical and mental function. The maximum possible score for each dimension is 100 and the minimum score is zero, with higher scores indicating better health. Knutsen et al (2004) reported that at two year follow-up, SF-36 physical component scores following MACI were significantly lower compared with scores following microfracture ($P=0.004$); however, this difference was not found at five year follow-up. This study reported that no significant difference in the SF-36 mental health subscale scores was detected between the groups two years after the procedure. Salzmann et al (2009) reported that SF-36 physical component scores following MACI (mean 52.4, SD 2.7) were not significantly different compared with scores following mosaicplasty (mean 48.8, SD 8.2). Similarly, this study reported that SF-36 mental component scores following MACI (mean 52.5, SD 3.4) were not significantly different compared with scores following mosaicplasty (mean 46.6, SD 8.8).

The EuroQuol Group 5-Dimension Self Report Questionnaire (EQ-5D) evaluates participants' health status 'today' along five dimensions: mobility, ability to undertake self-care, ability to participate in usual activities, pain/discomfort, and anxiety/depression. Derrett et al (2005) reported that the EQ-5D social tariff score was higher (better) for the

ACI group (mean 0.64) compared with the mosaicplasty group (mean 0.47); however, this difference did not reach statistical significance.

Pain scores

Three studies (one RCT and two comparative studies) were identified that compared pain scores for patients that underwent MACI/ACI with patients that underwent microfracture (Knutsen et al 2004), debridement (Fu et al 2005) or mosaicplasty (Salzmann et al 2009). All three studies used the Visual Analog Scale (VAS), where zero represents no pain and 10 represents the worst pain ever.

Knutsen et al (2004) reported that pain was significantly reduced in both groups ($P < 0.0001$ for both), with 78 per cent of ACI patients and 75 per cent of microfracture patients having less pain at two year follow-up compared with the baseline evaluation, and this improvement was maintained at five year follow-up. However, the two groups did not differ significantly with regard to pain scores at one, two, or five year follow-up. Similarly, Salzmann et al (2009) reported that VAS pain scores following MACI (mean 1.9, SD 0.8) were not significantly different compared with scores following mosaicplasty (mean 2.5, SD 2.2). Fu et al (2005) reported that at three year follow-up, the difference in pain scores from baseline was significantly higher in ACI patients (median 4, range 1-6) compared with debridement patients (median 0, range 0-2) ($P < 0.001$).

Imaging outcomes

Six studies (two RCTs and four comparative studies) were identified that compared imaging outcomes for patients that underwent MACI/ACI with patients that underwent microfracture (Knutsen et al 2004; Saris et al 2008; Welsch et al 2008a; Welsch et al 2008b; Welsch et al 2009) or mosaicplasty (Salzmann et al 2009). A variety of imaging outcome measures was used.

The biochemical evaluation of articular cartilage repair by MRI scans was reported in three studies which used T2-mapping for the assessment of the major ultrastructural components of cartilage: water, collagen, and glycosaminoglycans (Salzmann et al 2009; Welsch et al 2008a; Welsch et al 2009). Salzmann et al (2009) reported that T2 values for repair tissue following MACI (mean 46.8 ms, SD 8.6, range 35-57) were significantly lower when compared with T2 values after mosaicplasty (mean 55.5 ms, SD 6.7, range 48-68) ($P=0.048$). The study by Welsch et al (2008a) failed to provide statistical reporting on the difference in T2 values for cartilage repair tissue following microfracture (mean 47.3 ms, SD 10.3, range 33-64) compared with MACI (mean 56.4 ms, SD 9.6, range 45-72). Welsch et al (2008b) reported that mean T2 values showed significantly lower values for cartilage repair tissue produced after microfracture compared with cartilage repair tissue produced after MACI ($P=0.025$). Similarly, Welsch et al (2009) reported that T2 values for cartilage repair areas after microfracture (mean 47.9 ms, SD 9.8) were significantly lower compared with T2 values after MACI (mean 53.6 ms, SD 11.9) ($P=0.039$). Welsch et al (2008a), Welsch et al (2008b) and Welsch et al 2009 all reported that the cartilage repair tissue in patients after microfracture showed significantly reduced T2 values relative to that of healthy tissue, while cartilage repair tissue after MACI was not significantly different compared with healthy tissue.

Magnetisation Transfer (MT) imaging is an additional biochemical cartilage imaging tool, which is capable of detecting differences between healthy cartilage and areas of cartilage repair. Welsch et al (2008b) reported that although the mean MT ratio (MTR) for cartilage repair tissue after microfracture was lower compared with cartilage repair tissue after MACI, this difference was not statistically significant.

Diffusion-weighted imaging (DWI), which is an alternative biochemical MRI evaluation technique for the assessment of articular cartilage repair, was reported in one study (Welsch et al 2009). In this study, values for cartilage repair tissue showed no significant difference in diffusivity between microfracture (mean 1.50, SD 0.27) and MACI (mean 1.44, SD 0.24).

The morphological evaluation of articular cartilage repair tissue quality by MRI scans was reported in three studies which used the Magnetic resonance Observation of Cartilage Repair Tissue (MOCART) scale (maximum score achievable 100) (Salzmann et al 2009; Saris et al 2008; Welsch et al 2009). Salzmann et al (2009) reported that the MOCART score was not significantly different in the MACI and mosaicplasty groups. Saris et al (2008) reported that at 36 month follow-up, no significant difference was found between the ACI and microfracture groups regarding the preselected MOCART subscales considered reflective of cartilage repair quality (defect filling, repair tissue surface, subchondral lamina, subchondral bone reaction). Similarly, Welsch et al (2009) reported that no significant difference in MOCART score was found between the MACI (mean 75.5, SD 13, range 50-90) and microfracture groups (mean 75.0, SD 12, range 50-90).

The Kellgren and Lawrence grading system is a method of scoring and grading x-rays for the presence of osteoarthritis based on the degree of osteophyte (bone spur) formation, joint space narrowing, sclerosis (changing of the bone tissue around the joint), and joint deformity. Knutsen et al (2004) reported that at five year follow-up, no significant difference was found between the ACI and microfracture groups regarding the frequency of radiographic changes as measured on the Kellgren and Lawrence scale. However, this study did find an association between osteoarthritis (as measured on the Kellgren and Lawrence scale) and pain (as measured on the VAS) at five years ($P=0.035$), suggesting that patients with pain in the knee were more likely to have radiographic signs of early osteoarthritis. Similarly, an association between the SF-36 physical component score and radiographic evidence of osteoarthritis as measured by the distance between the femur and the tibia ($P=0.026$) was reported.

What are the economic considerations?

Economic evaluation of new health care technologies is important when determining whether the new initiative offers additional benefits and at what cost. Economic evaluations are able to determine whether the new initiative is dominated by (or dominates) the existing technology, such that the costs are higher (lower) and the effectiveness is less (greater). Economic evaluation is particularly important where the new initiative offers health benefits at additional costs. Within a constrained health care budget, determining the additional cost that would be paid for a given health gain is important when ascertaining whether such incremental costs represent value for money.

The usual process for an economic evaluation is first to determine the incremental effectiveness, which is the additional benefits associated with the new technology relative to current practice. Secondly, to determine the incremental costs, this is the difference in costs between the new initiative and current practice. Finally the incremental cost-effectiveness ratio (ICER) can be calculated using the following ratio:

$$ICER = \frac{Cost_{New} - Cost_{Comparator}}{Effectiveness_{New} - Effectiveness_{Comparator}}$$

The ICER can then be compared to a threshold, or range of thresholds, to determine whether the health system should invest in the new technology.

If the technology is just as effective as the existing technology, then a cost-minimisation approach is warranted.

Objective

The objective of this section was to conduct a costing analysis of MACI/ACI for hyaline cartilage damage in knee joints. The Advisory Panel advised that mosaicplasty and microfracture would be the most appropriate comparators for the costing analysis.

Search strategies

As described in the 'approach to assessment', a search strategy was developed to systematically identify studies in which MACI/ACI were used in the treatment of hyaline cartilage damage in knee joints.

Databases of peer-reviewed literature including Medline, PubMed, CINAHL and Cochrane were searched. The bibliographies of all retrieved publications were hand-searched for any relevant references which were not identified in the database search. Web-based searches included the Internet search engines 'Google' and 'Google scholar'.

In addition to the search terms described in the 'approach to assessment' section, Cost\$ or Econ\$ were added in order to identify any published cost-effectiveness analyses. The inclusion and exclusion criteria remained the same.

Background – evidence of cost-effectiveness

A number of cost-effectiveness analyses were identified in the literature.

Derrett et al (2005) published a cross-sectional retrospective comparison of ACI, mosaicplasty and a control group. In this study 53 ACI patients, 20 mosaicplasty patients and 22 patients waiting for ACI were compared. The average cost per patient was higher for ACI (£10,600; AUD\$18,130)¹ when compared to mosaicplasty (£7,948; AUD\$13,594). ACI patients tended to have better health status outcomes; however, these differences were not statistically significant. Compared to the option of waiting for ACI, the estimated average costs per quality-adjusted life year (QALY) were £23,043 for ACI and £66,233 for mosaicplasty, which translates to an incremental cost-effectiveness ratio for ACI relative to mosaicplasty of £16,349 per QALY gained. This study was limited and potentially biased by its design, since the patients were not randomly assigned to treatment groups. Consequently, the ACI patients tended to be younger, and therefore potentially had a greater capacity to benefit, than the mosaicplasty patients.

A UK HTA found that there was insufficient evidence to determine whether ACI was cost-effective compared with either microfracture or mosaicplasty (Clar et al 2005). Short-term modelling suggested that the quality of life gain from ACI versus microfracture would have to be between 70 to 100 per cent greater over two years for it to be more cost-effective². However, if the quality of life gains could be maintained over a longer period of time, the gains in effectiveness would not need to be so dramatic.

Finally, a technology appraisal by the National Institute for Health and Clinical Excellence (NICE 2008) concluded that the relative data on the effectiveness of ACI compared with microfracture or mosaicplasty was inconsistent. This finding was compounded by the lack of long-term follow-up data, and insufficient evidence supporting quality of life gains in patients treated with ACI compared to the alternative treatments.

Assumptions

- ACI and MACI are assumed to be equivalent.
- The comparators for MACI/ACI are mosaicplasty and microfracture.
- The clinical effectiveness of MACI/ACI, mosaicplasty and microfracture are identical.
- There is insufficient evidence to support differences in the use of rehabilitation health services following MACI/ACI, mosaicplasty or microfracture. Therefore, rehabilitation requirements following these procedures are assumed to be identical. Consequently, assessment costs and rehabilitation costs have not been considered during the cost analysis.

Estimate of cost

The estimated costs of MACI/ACI, mosaicplasty and microfracture were taken from a number of sources. These included the MBS, Australian Refined Diagnostic Related

¹ Average exchange rate for 2010 from the RBA where A\$1 = GBP£0.584665

² Cost-effectiveness threshold is equal to £20,000-30,000 per QALY

Group (AR-DRG) (D01Z version 5.1 round 11 – Private and Public), prosthesis list and the median charged Medicare fee.

Resource use and MBS item numbers were determined by the Advisory Panel.

Average costs per procedure

The MACI/ACI procedure is performed in two stages. Firstly, the patient is required to undergo a day procedure which involves an arthroscopic biopsy to remove a small piece of cartilage. Chondrocyte cells are isolated from the cartilage sample and cultured in a laboratory for four weeks. The second stage comprises an arthroscopy procedure, during which the collagen matrix-embedded chondrocyte cells are implanted into the lesion.

Cell culture and prosthesis costs

The costs related to the isolation and growth of chondrocyte cells are based on the current prosthesis list price. According to the August 2010 prosthesis list, autologous chondrocyte transplantation costs \$11,400. In addition to this cost, the chondrocyte cells are sealed into position using fibrin glue (Tisseel, Baxter Healthcare). Fibrin glue is TGA-listed and costs \$380 per 1 mL syringe (August 2010 prosthesis list). These prosthesis costs are unique to MACI/ACI and therefore do not apply to mosaicplasty or microfracture.

The mosaicplasty procedure requires a specific surgical kit. It was estimated by the Applicant that this kit costs \$1,000. However, this could not be verified during the evaluation.

MBS items

The MBS item fees, which represent the Australian Government contribution to each procedure, were obtained from MBS Online. The patient usually receives a reimbursement of 75 per cent of the schedule fee for inpatient services and 85 per cent for outpatient services. Consequently, the benefit amount and not the full MBS fee were used in the model, as using the full fee would double count some of the copayment contribution.

Average copayments

Average copayments were provided by the Department of Health and Ageing. The copayment component is calculated as the fee charged minus the MBS benefit paid plus any additional specialist fees. The copayment may not be the exact patient contribution, since it may also include some insurance contribution (up to 25 per cent of the MBS fee). To avoid double counting, the 25 per cent insurance contribution is not included as a separate cost. The copayments are calculated as averages of all procedures claimed under the item number. Consequently, there may be a degree of heterogeneity in services claimed under each item. Therefore the accuracy of the copayment is dependent on the other procedures that are also claimed under the same item number.

Hospital stay

The average per diem cost for hospitalisation was derived from the AR-DRG information for DRG I8Z (version 5.1 round 12 – Private and Public) for ‘other knee procedures’. To calculate the per diem cost, the direct and overhead ward nursing costs plus hotel costs were divided by the DRG average length of stay. As suggested by the Advisory Panel, two nights of hospital stay would be necessary for MACI/ACI.

Proposed fee

The proposed MBS fees for MACI/ACI are based on two current MBS items. The initial biopsy of chondrocyte cells is based on MBS 49557, which is the MBS item fee for diagnostic knee arthroscopy (\$257.95). The arthroscopic chondrocyte grafting procedure is based on MBS 49563, which is the MBS item fee for arthroscopic knee surgery involving chondral grafting (\$752.95). The rationale for using these existing MBS items is based on the fact that they adequately reflect the amount of time and experience required to perform a MACI/ACI procedure. However, it should be noted that the actual surgical time is dependent on the lesion size and location.

Table 10 Calculation of the average cost per knee

	MACI/ACI		Mosaicplasty		Microfracture		Source
	units	costs	units	costs	units	costs	
Equipment							
Autologous chondrocyte transplantation	1	\$11,400.00					Prostheses List
TISSEEL fibrin sealant syringe	1	\$380.00					Prostheses List
Surgical kit			1	\$1,000.00			Applicant
Operational							
Pre-anaesthesia consultation - MBS 17610	2	\$30.45	1	\$30.45	1	\$30.45	MBS Online
Co-payment	2	\$30.17	1	\$30.17	1	\$30.17	DOHA
Initiation anaesthesia - MBS 21382	2	\$56.10	1	\$56.10	1	\$56.10	MBS Online
Co-payment	2	\$208.33	1	\$208.33	1	\$208.33	DOHA
Biopsy - MBS 49557	1	\$193.50					MBS Online
Anaesthesia - MBS 23061	1	\$84.15					MBS Online
Assistance - MBS 51300	1	\$61.20					MBS Online
Co-payment	1	\$0.00					DOHA
Osteochondral graft - MBS 49563*	1	\$564.75	1	\$564.75			MBS Online
Anaesthesia - MBS 23063	1	\$84.15	1	\$84.15			MBS Online
Assistance - MBS 51303	1	\$112.95	1	\$112.95			MBS Online
Co-payment	1	\$97.89	1	\$97.98			DOHA
Arthroscopic surgery - MBS 49561					1	\$477.80	MBS Online
Anaesthesia - MBS 23043					1	\$56.10	MBS Online
Assistance - MBS 51300					1	\$61.20	MBS Online
Co-payment					1	\$30.81	DOHA
Hospital stay (2,2,1)	1	\$454.05	1	\$454.05	1	\$227.03	AR-DRG I18Z
Consumables		\$11,780.00		\$1,000.00		\$0.00	
MBS fees		\$1,273.80		\$1848.40		\$908.68	
Out-of-pocket		\$1,028.95		\$790.45		\$496.34	
TOTAL COSTS		\$14,082.75		\$2,638.85		\$1,405.01	

*The cost of chondrocyte implantation is based on a single focal lesion. Complex and multiple lesions may incur additional costs.
ACI: autologous chondrocyte implantation; AR-DRG I18Z: Australian Refined Diagnostic Related Group; DOHA: Department of Health and Ageing;
MACI: matrix-induced autologous chondrocyte implantation; MBS: Medicare Benefits Schedule.

Average costs per knee

The total estimated cost of performing the MACI/ACI (biopsy and grafting) procedure is \$14,083 per knee. The comparative costs associated with mosaicplasty and microfracture are \$2,639 and \$1,405, respectively (Tables 10 and 11). The incremental cost of MACI/ACI as opposed to mosaicplasty is \$11,444 and as opposed to microfracture is \$12,678.

The main difference between the cost of the MACI/ACI, mosaicplasty and microfracture procedures is the cost of the chondrocyte cell culture and Tisseel sealant (\$11,400+\$380). There are also additional costs associated with the additional biopsy procedure, but these are offset somewhat by the mosaicplasty surgical kit.

Table 11 Incremental cost

	MACI/ACI	Mosaicplasty	Microfracture
Consumables	\$11,780.00	\$1,000.00	\$0.00
MBS fees	\$1,273.80	\$848.40	\$908.68
Out-of-Pocket	\$1,028.95	\$790.45	\$496.34
TOTAL COSTS	\$14,082.75	\$2,638.85	\$1,405.01
Incremental cost (MACI/ACI v)		\$11,443.90	\$12,677.73

ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation; MBS: Medicare Benefits Schedule

Implication to the Extended Medicare Safety Net

Compared to mosaicplasty, five additional MBS items are required for MACI/ACI. These items pertain to the additional biopsy procedure (items 49557, 23061 and 51300) and the associated anaesthesia (items 17610 and 21382). However, all MBS items are performed in the inpatient setting; therefore, any out-of-pocket costs associated with these items will not contribute towards the Extended Medicare Safety Net (EMSN). Consequently, out-of-pocket contributions for MACI/ACI are unlikely to impact upon the EMSN.

Financial implications

The prevalence and incidence rates for hyaline cartilage damage in knee joints are unclear. The rates are difficult to estimate because cartilage defects may occur indirectly, months or years after an initial injury.

The number of potential candidates suitable for MACI/ACI can be estimated in a number of ways. For the primary analysis the number of procedures currently performed in Australia was estimated using 2005-06 and 2008-09 MBS codes for knee arthroscopic surgery involving osteochondral or chondral grafts (49563). In 2005-06 there were 1,007 procedures claimed under Medicare and in 2008-09 934 procedures were claimed. Therefore for the base case analysis it is assumed that 1,000 patients per year are suitable for MACI/ACI procedures.

A sensitivity analysis was conducted, in which the potential wider pool of patients was calculated. Aroen et al (2004) conducted an analysis of all patients undergoing knee arthroscopy during a six month period in three hospitals in Oslo, Norway. The median age of the patient population was 35 years. Of the 933 consecutive knee arthroscopies analysed, 11 per cent had cartilage defects that may be suitable for cartilage repair procedures. Therefore an upper estimate of the patients suitable for MACI/ACI was estimated as being 11 per cent of all arthroscopies currently performed in Australia. The

number of knee procedures (other than replacement and recapping) performed in private hospitals in Australia in 2008-09 was 64,237 (AR-DRG I18Z 2008-09). Therefore if 11 per cent of these patients are suitable for a cartilage repair procedure, a total of 7,066 MACI/ACI procedures could potentially be performed per year.

Table 12 Financial impact – base case

	MACI/ACI	Mosaicplasty	Microfracture
Total cost per patient	\$14,083	\$2,639	\$1,405
Number of patients	1000	1000	1000
<i>Breakdown of financial implications:</i>			
Consumables	\$11,780,000	\$1,000,000	\$0
MBS items	\$1,273,800	\$848,400	\$908,677
Patient out-of-pocket	\$1,028,946	\$790,446	\$496,335
Total financial implications	\$14,082,746	\$2,638,846	\$1,405,012
<i>Incremental costs:</i>			
Consumables		\$10,780,000	\$11,780,000
MBS items		\$425,400	\$365,123
Patient out-of-pocket		\$238,501	\$294,111
Total cost		\$11,443,901	\$12,677,734

ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation; MBS: Medicare Benefits Schedule

Based on these data (Table 12), the estimate total cost of providing 1,000 MACI/ACI procedures would be \$14.08 million per annum. The equivalent total cost for microfracture would be \$1.41 million. Therefore if MACI/ACI was used instead of microfracture for all 1,000 patients, the incremental total cost would be \$12.68 million. The vast majority of this additional cost is attributed to the chondrocyte cell culture procedure. However, because MACI/ACI requires an extra biopsy procedure, there would still be an estimated \$365,123 additional cost to the MBS.

Table 13 Financial impact – worst case

	MACI/ACI	Mosaicplasty	Microfracture
Total cost per patient	\$14,083	\$2,639	\$1,405
Number of patients	7066	7066	7066
<i>Breakdown of financial implications:</i>			
Consumables	\$83,237,480	\$7,066,000	\$0
MBS items	\$9,000,671	\$5,994,794	\$6,420,712
Patient out-of-pocket	\$7,270,536	\$5,585,291	\$3,507,105
Total financial implications	\$99,508,687	\$18,646,086	\$9,927,817
<i>Incremental costs:</i>			
Consumables		\$76,171,480	\$83,237,480
MBS items		\$3,005,876	\$2,579,959
Patient out-of-pocket		\$1,685,245	\$2,078,186
Total cost		\$80,862,601	\$89,580,870

ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation; MBS: Medicare Benefits Schedule

The worst case scenario represents the potential unmet demand of hyaline cartilage damage in knee joints. Based on these data (Table 13), the estimate total cost of providing 7066 MACI/ACI procedures would be approximately \$99.51 million per annum. The equivalent total cost of microfracture would be approximately \$9.93 million. Therefore if MACI/ACI was used instead of microfracture for all 7066 patients, the incremental total cost would be over \$89.58 million. Of this, the estimated additional cost to the MBS would be \$2.58 million.

Cost-effectiveness

The objective of the economic evaluation was to compare the cost-effectiveness of MACI/ACI relative to mosaicplasty and microfracture. In the absence of conclusive effectiveness data, a cost analysis was conducted to compare the different costs associated with each of the three procedures.

The estimated costs of MACI/ACI, mosaicplasty and microfracture were taken from a number of sources, including the MBS, AR-DRG cost, prosthesis list and the median charged MBS fee.

Based on a number of estimates and assumptions:

- the total estimated cost of MACI/ACI is \$14,083 per knee. The comparative cost associated with mosaicplasty is \$2,639 and with microfracture is \$1,405. The incremental cost of MACI/ACI relative to mosaicplasty is \$11,444 and relative to microfracture is \$12,678.
- Based on current MBS utilisation data, the estimated total cost of providing 1,000 MACI/ACI procedures would be \$14,082,746 per annum, compared to \$1,405,012 for the equivalent number of microfracture procedures. Therefore if MACI/ACI was used instead of microfracture for all 1,000 patients, the incremental total cost would be \$12,677,734 per annum. Of this, an estimated \$365,123 additional cost would be attributed to the MBS.

What are the other considerations?

Consumer considerations

There are several issues that patients need to be aware of when considering MACI/ACI as a treatment for articular cartilage defects.

Need for multiple operations

The MACI/ACI procedure involves two operations, compared with one operation for the comparator procedures of mosaicplasty and microfracture. This may increase the risk of adverse events.

Rehabilitation requirements

The clinical expert opinion of the Advisory Panel suggests that the rehabilitation time following MACI/ACI and the comparator procedures of mosaicplasty and microfracture is broadly equivalent, with recovery taking at least 12 months. However, it is important to note that there is a lack of well-controlled studies describing the optimum postoperative rehabilitation protocols and guidelines regarding return to full activity, for patients following surgical treatment for articular cartilage defects.

Cost and equity of access issues

The major costs associated with the MACI/ACI procedure are the costs of the chondrocyte cell culture and the Tisseel sealant (\$11,780), which are borne by the patient and do not apply to the mosaicplasty or microfracture procedures. Given the complexity of the MACI/ACI procedure, it is unlikely that it will be offered widely. Additionally, in order for a patient to be eligible for the MACI/ACI procedure, a formal diagnosis through MRI or arthroscopy is required. Both of these factors raise the issue of equity of access for this procedure.

Discussion

Limitations of the evidence

This review, examining the safety and effectiveness of MACI and ACI for the treatment of articular cartilage defects, was limited by the available evidence. Whilst the evidence base was not limited by the quantity of studies, it was limited in regards to the quality of the available studies. Specifically, the studies available for this assessment were heterogeneous in terms of the patients recruited, the MACI/ACI technique used and the measures used to assess patient outcomes, which made it difficult to draw direct comparisons between the different procedures across studies.

Patient characteristics such as age and lesion size varied between studies. Some studies included patients who had undergone previous treatments, including bone marrow stimulation by drilling, abrasion or microfracture, while others included patients with no previous surgical treatments. It is important to note that previous surgical treatments can impact on patient outcomes following the MACI/ACI procedure. It is possible that residue from previous repair tissue could influence in a paracrine manner the biological properties of new implants introduced by MACI/ACI, thus biasing patient responses to the procedure.

Multiple scoring systems were used to assess knee function. The variety of scales observed in the literature suggests that for functional outcomes, there is no standard outcome which can be used as a measure of effectiveness following surgical treatment for articular cartilage defects. Given the variety of scoring systems used, developing a global outcome of knee function by converting existing scores was challenging. In addition, reporting the improvement in functional outcomes compared with preoperative values was not possible, as not all studies reported patient scores at baseline.

Rehabilitation is an important consideration when assessing patient outcomes following surgical treatment for articular cartilage defects. A number of the included studies did provide a description of the rehabilitation protocol that patients were required to complete following surgery; however, few studies reported on patient compliance with these protocols, which is a factor that is likely to have impacted on functional outcomes.

A further limitation of the studies included in this assessment was the length of follow-up reported. It has been suggested that any differences in outcome based on formation of articular rather than fibrocartilage in the defect may be quite subtle and may only reveal themselves after many years of follow-up (five to 10 years). However, the majority of studies in this assessment reported short to medium-term (one to three years) follow-up of patients.

An overall evaluation of the body of evidence for MACI and ACI for the treatment of articular cartilage defects in patients requiring treatment for articular cartilage defects is presented in Table 14.

Table 14 Body of evidence assessment matrix for MACI/ACI

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base			Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact		Substantial		
Generalisability		Population/s studied in the body of evidence are similar to the target population		
Applicability		Applicable to Australian healthcare context with few caveats		

Adapted from NHMRC (2009)

ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation.

Safety

Overall, safety data was not reported as comprehensively as effectiveness outcomes in the included comparative studies, with few studies reporting statistical comparisons between MACI/ACI and comparator procedures. This may represent study bias where the primary concern of the authors was to present data on effectiveness, rather than safety.

For the majority of adverse events reported, there were no obvious differences in incidence rates between the MACI/ACI and comparator procedure groups. However one study reported that the incidence of joint swelling and joint crepitation was significantly higher following ACI compared with microfracture. Similarly, the incidence rates for joint effusion and tissue hypertrophy (both symptomatic and asymptomatic) appeared higher following MACI/ACI than following comparator procedures. Procedure failure rate was the most commonly reported adverse event, and demonstrated an incidence rate of 9.5 per cent in the MACI/ACI population, and 11.9 per cent in the comparator procedure population.

Major adverse events such as joint infection and deep vein thrombosis were rare in both the MACI/ACI and comparator groups, and there were no reported deaths as a result of the procedures in either group.

Overall, the safety of MACI/ACI appears to be comparable to those comparator procedures evaluated in this assessment.

Effectiveness

Functional outcomes were the focus of the majority of included studies; however, a number of studies also reported imaging outcomes following MACI/ACI and comparator procedures.

As mentioned earlier, a variety of scoring systems were used to assess knee function, which made it difficult to draw direct comparisons between the different procedures across studies. The most commonly reported functional outcome measures were the Lysholm and Tegner scores. Of the eight studies that reported Lysholm scores, six reported no significant difference in the effectiveness of MACI/ACI over time compared with comparator procedures; however, one study each reported that MACI/ACI was more effective over time compared with microfracture and mosaicplasty. Similarly, of the five studies that reported Tegner scores, four studies reported no significant difference in the effectiveness of MACI/ACI over time compared with comparator procedures; however, one study reported that MACI was more effective over time compared with microfracture.

Most studies that assessed these outcomes reported that quality of life and pain scores were not significantly different following MACI/ACI compared with comparator procedures; however, one study did report that the improvement in pain scores following ACI was significantly better compared with debridement.

Imaging outcomes, reported in a limited number of studies, revealed no significant difference in the quality of articular cartilage repair following MACI/ACI compared with comparator procedures. Similarly, one study reported that at five year follow-up, there was no significant difference in the frequency of radiographic changes that were indicative of osteoarthritis in MACI/ACI patients compared with patients who underwent microfracture.

Overall, in the short to medium term, the effectiveness of MACI/ACI appears to be comparable to those comparator procedures evaluated in this assessment.

Cost-effectiveness

A full economic evaluation was not undertaken because of the lack of evidence supporting the superior effectiveness of MACI/ACI. The results of the costing analysis demonstrated that MACI/ACI is more costly than either microfracture or mosaicplasty. The reason for the additional cost is two-fold. Firstly, MACI/ACI require two separate surgical procedures, the first to biopsy the chondrocyte cells and the second to implant the cultured cells. Mosaicplasty and microfracture only require a single procedure. Therefore the extra procedure has flow-on costs in terms of additional MBS items and patient co-payments. Secondly, MACI/ACI requires the isolation and growth of chondrocyte cells in tissue culture. This cost is significant and adds an extra \$11,400 per knee repaired.

Precise identification of the number of patients eligible for MACI/ACI was difficult, and two estimates were calculated. The first estimate was based on the number of patients currently undergoing hyaline cartilage repair. The second estimate was based on the potential number of patients suitable for cartilage repair, this being an estimate of the unmet demand for MACI/ACI. The financial implications were indicative only, since they assumed a 100 per cent switch from mosaicplasty or microfracture to MACI/ACI.

The actual uptake rate of MACI/ACI was not estimated because of the uncertainty around this value.

Patient characteristics and damage pathology were not considered. As suggested by the Advisory Panel, the size and number of lesions may influence the preferred treatment options. Also not considered was the possibility of using MACI/ACI as a second line treatment in patients who had previously failed either microfracture or mosaicplasty.

Conclusions

The aim of the review was to evaluate the safety, effectiveness and economic implications of MACI and ACI for the treatment of articular cartilage defects. The conclusions that could be drawn from this review were limited by the quantity and quality of the evidence. Based on these studies, it appears that the MACI/ACI procedure is relatively safe, and is not associated with serious adverse events; however, the clinical expert opinion of the Advisory Panel suggests that patients need to be aware that as the MACI/ACI procedure involves two operations, compared with one operation for comparator procedures, it may be associated with a higher rate of adverse events. In the short to medium term, the effectiveness of MACI/ACI in terms of functional, pain and quality of life outcomes appears to be comparable to those comparator procedures evaluated in this assessment. However, it should be noted that neither MACI/ACI nor the comparator procedures have been reliably shown to be superior to non-surgical treatments in properly constructed RCTs. Furthermore, MACI/ACI is not routinely performed in the Australian public hospital system, where the availability of item numbers is not an issue. A costing analysis demonstrated that MACI/ACI is significantly more expensive than either microfracture or mosaicplasty for the repair of knee hyaline cartilage damage. The additional cost is mostly due to the chondrocyte cell culture procedure. Based on current MBS utilisation data, it was estimated that approximately 1,000 patients undergo hyaline knee cartilage repair per annum. The estimate total cost of providing 1,000 MACI/ACI procedures per year would be \$14,082,746 per annum, compared to \$1,405,012 for the equivalent number of microfracture procedures. Therefore if MACI/ACI was used instead of microfracture for all 1,000 patients, the incremental cost would be \$12,677,734 per annum. Of this, an estimated \$365,123 additional cost would be attributed to the MBS. These estimates assume a 100 per cent uptake rate of MACI/ACI.

Appendix A MSAC terms of reference and membership

The Medical Services Advisory Committee (MSAC) is an independent scientific committee comprising individuals with expertise in clinical medicine, health economics and consumer matters. It advises the Minister for Health and Ageing on whether a new medical service should be publicly funded based on an assessment of its comparative safety, effectiveness, cost-effectiveness and total cost, using the best available evidence. In providing this advice, MSAC may also take other relevant factors into account. This process ensures that Australians have access to medical services that have been shown to be safe and clinically effective, as well as representing value for money for the Australian health care system.

MSAC is to:

- Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures, in relation to:
 - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
 - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
 - the proposed MBS item descriptor and fee for the service where funding through the MBS is supported;
 - the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
 - other matters related to the public funding of health services referred by the Minister.
- Advise the Australian Health Minister's Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to such sub-committees.

The membership of MSAC at the December 2010 meeting comprised a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Professor Robyn Ward (Chair)	Medical Oncology
Associate Professor Frederick Khafagi (Deputy Chair)	Nuclear Medicine
Professor Jim Butler (Chair, Evaluation Sub-committee)	Health Economics
Associate Professor John Atherton	Cardiology
Professor Justin Beilby	General Practice/Research
Associate Professor Michael Bilous	Anatomical Pathology
Professor Jim Bishop AO	Chief Medical Officer (<i>ex officio member</i>)
Professor Peter Cameron	Trauma and Emergency Medicine
Associate Professor Kirsty Douglas	General Practice/Research
Professor Kwun Fong	Thoracic Medicine
Professor Richard Fox	Medical Oncology
Professor John Horvath	Renal Medicine/Health Workforce
Ms Elizabeth Koff	Health Administration
Professor Helen Lapsley	Health Economics
Professor Peter McCluskey	Ophthalmology
Mr Russell McGowan	Consumer Health Representative
Dr Allan McKenzie	Radiology
Dr Graeme Suthers	Genetics/Pathology
Mr David Swan	AHMAC Representative (<i>ex officio member</i>)
Professor Ken Thomson	Radiology
Dr Christine Tippett	Obstetrics/Gynaecology
Associate Professor David Winlaw	Paediatric Cardiothoracic Surgery

Appendix B Advisory panel and evaluators

Advisory panel for MSAC Application 1140: Matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation

Member	Nomination/Expertise or Affiliation
Professor Peter Cameron	Chair, member of MSAC
Dr Caroline Wright	Deputy Chair, member of MSAC (following resignation of Dr Shiong Tan)
Associate Professor David Morgan	Australian Orthopaedic Association nominee
Associate Professor John Hart	Australian Orthopaedic Association nominee
Dr Geoff Markov	Royal Australasian College of Physicians nominee
Professor Nick Fazzalari	Head, Bone and Joint Research
Dr Janet Wale	Consumers' Health Forum of Australia nominee
Mr Isaac Hudson	Project Manager

Evaluation Sub-committee input

Member	Nomination/Expertise or Affiliation
Professor Jim Butler	Member of MSAC, member of Evaluation Sub-Committee

Evaluators

Name	Organisation
Mr Luis Zamora	ASERNIP-S
Dr Prema Thavaneswaran	ASERNIP-S
Ms Karen Humphreys	ASERNIP-S
Dr Alun Cameron	ASERNIP-S
Dr Stephen Goodall	CHERE

Appendix C Approach to assessment

Search strategy

Table 15 Bibliographic databases searched

Electronic Database	Time period and search limits
Cochrane Library – including: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, NHS Economic Evaluation Database	Inception – March 2010
EMBASE	Inception – March 2010
Medline	Inception – March 2010

Table 16 Electronic internet databases searched

Electronic Database	Internet address
Centre for Reviews and Dissemination (CRD) / International Network of Agencies for Health Technology Assessment (INAHTA) databases – including: NHS Economic Evaluation Database (NHS EED) / Database of Abstracts of Reviews of Effect (DARE) / Health Technology Assessment (HTA) Database	http://www.york.ac.uk/inst/crd/
National Health and Medical Research Council (NHMRC) (Australia)	http://www.nhmrc.gov.au/
Australian Department of Health and Ageing	http://www.health.gov.au/
Scirus – for Scientific Information Only	http://www.scirus.com
TRIP database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services / Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/pages/grey_literature_report
US Department of Health and Human Services (reports and publications)	http://www.hhs.gov/

Table 17 Health technology assessment internet sites

Argentina
Institute for Clinical Effectiveness and Health Policy (IECS) http://www.iecs.org.ar/iecs-visor-publicaciones-ing.php
Australia
Adelaide Health Technology Assessment (AHTA) http://www.adelaide.edu.au/ahta/
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/racs/research-and-audit/asernip-s.aspx
Centre for Clinical Effectiveness, Monash University http://www.southernhealth.org.au/page/Health_Professionals/CCE/
Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au/centres/che/
Medical Services Advisory Committee (MSAC) http://www.msac.gov.au
Austria
Institute of Technology Assessment (ITA) http://www.oew.ac.at/ita/e1-3.htm
Brazil
Departamento de Ciência e Tecnologia (DECIT) http://portal.saude.gov.br/portal/saude/area.cfm?id_area=1088
Canada
Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?home
Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home
Canadian Association for Health Services and Policy Research (CAHSR) http://www.cahsr.ca
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepe.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
Institute of Health Economics (IHE) http://www.ihe.ca/
Ministry of Health and Long-Term Care – Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html
Denmark
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) http://www.dacehta.dk
Danish Institute for Health Services Research (DSI) http://www.dsi.dk/english/
Finland
Finnish Office for Health Technology Assessment (FinOHTA) http://finohta.stakes.fi/EN/index.htm
France
Committee for Evaluation and Diffusion of Innovative Techniques (CEDIT) http://cedit.aphp.fr/english/index_present.html
French National Authority for Health (HAS) http://www.has-sante.fr
Germany
German Agency for Health Technology Assessment (DAHTA) http://www.dimdi.de/dynamic/en/hta/db/index.htm
Hungary
Unit of Health Economics and Technology Research Assessment (HunHTA) http://hecon.uni-corvinus.hu/corvinus.php?lng=en
The Netherlands
Health Council of the Netherlands Gezondheidsraad http://www.gezondheidsraad.nl/en
Netherlands Organisation for Health Research and Development (ZonMw) http://www.zonmw.nl/en/
New Zealand
New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

Table 17 (continued) Health technology assessment internet sites

Norway
Norwegian Knowledge Centre for the Health Services http://www.kunnskapscenteret.no
Spain
Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud Carlos III / Health Technology Assessment Agency (AETS) http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
Andalusian Agency for Health Technology Assessment (AETSA) http://www.juntadeandalucia.es/index.html
Catalan Agency for Health Technology Assessment (CAHTA) http://www.gencat.cat/salut/depsan/units/aatrm/html/en/dir394/index.htm
Sweden
Swedish Council on Technology Assessment in Healthcare (SBU) http://www.sbu.se/en/
Center for Medical Health Technology Assessment http://www.cmt.liu.se/?l=en
Switzerland
Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/
United Kingdom
NHS Quality Improvement Scotland http://www.nhshealthquality.org/nhsqis/CCC_FirstPage.jsp
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.nchta.org/
University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
National Institute for Health and Clinical Excellence (NICE) http://www.nice.org.uk
United States
Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/
US Blue Cross/ Blue Shield Association Technology Evaluation Centre (TEC) http://www.bcbs.com/betterknowledge/tec/
Veterans' Affairs Technology Assessment Program (VATAP) http://www4.va.gov/vatap/

Inclusion criteria

Table 18 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies and systematic reviews will be included. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies will be excluded. Comparative studies shall be used for safety and effectiveness outcomes. Non-comparative evidence will be used for safety outcomes alone. Larger case series of 10 or more consecutively-enrolled patients will be used in preference, in order to reduce bias. Case reports of individual patients will be excluded.
Patient	Patients of age 15-55 years with osteochondritis dissecans and / or acute cartilage defects of the knee, who have undergone arthroscopic lavage and debridement. Patients who have rheumatoid arthritis, inflammatory arthritis or osteoarthritis will be excluded. Patients who are obese, and patients who have instability or misalignment of the knee, will be excluded.
Intervention	Autologous chondrocyte implantation / transplantation; matrix-induced autologous chondrocyte implantation / transplantation (either with a periosteum patch or an inert porcine collagen membrane (Genzyme-patented)).
Comparator	Mosaicplasty, microfracture or debridement.
Outcome	All outcomes of clinical value will be included, including patient-related outcomes (such as QALYs) and imaging outcomes. Short-term and long-term outcomes will be reported. All adverse events and complications shall be reported or summarised. Histological outcomes shall be excluded. Where possible, outcomes shall be reported according to patient age, level of activity, size of original defect, location of original defect. Outcomes will be meta-analysed where appropriate.
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than English language articles. Translation of such articles will significantly increase the timeframe of the review.

Search terms

The following search strategy was used:

- #1 Chondrocytes [MeSH]
- #2 Chondrogenesis [MeSH]
- #3 Transplantation, Autologous [MeSH]
- #4 autologous chondrocyte implant* (textword)
- #5 ACI (textword)
- #6 MACI (textword)
- #7 autologous chondrocyte transplant* (textword)
- #8 ACT (textword)
- #9 ChondroCelect (textword)
- #10 TGX001 (textword)
- #11 TiGenix (textword)
- #12 BioPart II (textword)
- #13 ProChon Biotech (textword)
- #14 CARTIPATCH (textword)
- #15 TBF Genie Tissulaire (textword)
- #16 INSTRUCT (textword)
- #17 CellCo Tec BV (textword)
- #18 Genzyme (textword)
- #19 Merci (textword)
- #20 cartilag* (textword)
- #21 (#1 OR #9) AND #2
- #22 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
OR #15 OR #16 OR #17 OR #18 OR #19
- #23 #21 OR #22
- #24 #23 AND #20

Appendix D Critical appraisal of randomised controlled studies

Table 19 Critical appraisal summary of randomised controlled trials: study design details

Study	Sample size	Participants	Randomisation details	Blinding	Interventions and outcomes
Level II RCTs					
Basad et al 2010	Total: 60 MACI: 40 Microfracture: 20	Inclusion criteria provided. Exclusion criteria provided. MACI group was twice the size of MF group due to the combining of the two MACI groups planned in the original protocol. MF patients had higher mean BMI (27.3 vs 25.3 for MACI patients) and mean age (37.5 vs 33 for MACI). The only significant difference between MACI and MF groups was symptom duration, which was 0.3 years longer in the MF group (no <i>P</i> -value provided).	Randomisation through computer-generated randomisation list (no further details provided). Patients were allocated consecutive numbers in the order of their study entry and then randomised to receive either MACI or MF via a computer-generated randomisation list. No details of concealment.	Blinding not reported.	MACI intervention well detailed. MF intervention poorly detailed. Outcome measures were the Tegner (activity levels), Lysholm (pain, stability, gait, clinical symptoms) and ICRS scores. MRI scans were taken 1 week postoperatively to check for delamination and graft hypertrophy. Adverse events were also reported upon. Original study protocol called for arthroscopic biopsy of each defect 1 year after treatment; however, the decision was taken not to continue with this protocol requirement.
Bentley et al 2003	Total: 100 ACI: 58 Mosaicplasty: 42	Inclusion criteria: patients with symptomatic lesions of the articular cartilage of the knee. Exclusion criteria: not provided. Groups well matched for age (mean 31.6 years for ACI vs 30.9 years for mosaicplasty). Groups not well matched for aetiology or anatomical sites: proportion of ACI patients vs mosaicplasty patients with osteochondritis dissecans and chondromalacia patellae was at least double. Proportion of ACI	Initially, an arthroscopy was carried out. If the lesion was suitable for cartilage grafting, randomisation was undertaken by using random sample numbers in sealed envelopes. A total of 100 consecutive patients were randomised to have either mosaicplasty or ACI. No details of concealment.	Blinding not reported.	ACI intervention well detailed. Mosaicplasty intervention well detailed. Outcome measures were the modified Cincinnati rating system and the Stanmore functional rating system. Authors stated that there was no difference in the results when using either system, and it appears that the Cincinnati rating was used in preference to the Stanmore system for outcomes reporting (patients

		<p>patients vs mosaicplasty patients with defects of the patella or the lateral femoral condyle was at least double.</p> <p>All but 6 patients had undergone previous surgical interventions, but unclear whether this is evenly distributed between the groups.</p>			<p>with excellent and good results had improvement, those with fair results were unchanged and those with poor results were worse than before operation). Patients also received arthroscopy and biopsy at one year follow-up, with repair assessed using the International Cartilage Research Society (ICRS) grading system.</p> <p>Adverse events were also reported upon.</p>
Dozin B et al 2005	<p>Total: 47 ACI: 22 Mosaicplasty: 25</p>	<p>Inclusion criteria provided. Exclusion criteria provided.</p> <p>Patients were well matched for age, BMI, lesion site, lesion size and lesion grade. ACI group contained more men than women (77.3% vs 22.7%) while the mosaicplasty group contained similar proportions (45.5% vs 54.5%). Authors stated that besides gender, no remarkable differences were seen between the two arms.</p>	<p>Random treatment assignment was performed on the basis of random lists stratified by orthopaedic surgeon and balanced in permuted blocks of varying block size in random sequence. After verification of eligibility criteria, the treatment assignment (ACI or mosaicplasty) was communicated by phone to the orthopaedic surgeon.</p> <p>Random lists were kept at the Coordinating Centre, and the clinical investigators were unaware of the sequence of the assignments.</p>	<p>Patients were not blinded to the treatment assignment. No other details on blinding were reported.</p>	<p>ACI intervention well detailed. Mosaicplasty intervention well detailed.</p> <p>Outcome measures were the Lysholm Knee Scoring Scale (LKSS) and the Standard International Knee Documentation Committee (IKDC) Evaluation Form. The authors stated that there were no appreciable differences in the results when using either system, and to avoid redundancy the final results were presented only on the basis of the LKSS, with ratings categorised as complete success (>90), partial success (60-90), or failure (<60).</p>
Horas et al 2003	<p>Total: 40 ACI: 20 Autologous osteochondral cylinder (AOC): 20</p>	<p>Inclusion criteria provided. Exclusion criteria provided.</p> <p>The AOC group had almost twice as many men as the ACI group (15 vs 8). AOC patients were older than ACI patients (mean 35 years vs mean 31</p>	<p>Patients were randomly assigned to either group, with an alternating consecutive selection, after they had provided informed consent.</p> <p>No details of concealment.</p>	<p>The histological sections were evaluated by pathologists blinded to patient allocation.</p>	<p>ACI intervention well detailed. AOC intervention well detailed.</p> <p>Outcome measures were evaluated with use of a modification of the Lysholm, Tegner, and Meyers scores.</p>

		years). AOC patients were heavier than ACI patients (mean 80 kg vs mean 71 kg). AOC patients had smaller lesions than ACI patients (3.63 cm ² vs 3.86 cm ²) although authors stated that the difference between these sizes was not significant. The pre-operative Lysholm, Tegner, and Meyers scores were similar between the two treatment groups ($P < 0.12$).			Adverse events were also reported upon.
Knutsen et al 2004 ^a	Total: 80 ACI: 40 Microfracture: 40	Inclusion criteria provided. Exclusion criteria provided. ACI defects were larger than microfracture defects (mean 5.1 cm ² vs mean 4.5 cm ²). The groups appeared well matched for mean age, weight and number of previous operations. According to Knutsen et al 2004, preoperatively, no significant differences were found between the ACI and microfracture groups with regards to age, sex, defect size, body weight, or baseline clinical data.	With the use of sealed envelopes, patients who fulfilled the inclusion criteria were randomised during the arthroscopy to be treated with either ACI or microfracture. No details of concealment.	Histological examination was performed by a pathologist and a clinical scientist. Both were blinded to the type of treatment that the patient had received.	ACI intervention detailed. Microfracture intervention detailed. Outcome measures were clinical data using the Lysholm and Tegner scores, SF-36 physical component score and the visual analog pain scale. Adverse events were also reported upon.
Saris et al 2008 ^b	Total: 118 ACI: 57 Microfracture: 61	Inclusion criteria provided. Exclusion criteria provided. The treatment groups were well matched for patient baseline characteristics. The median duration of symptoms was longer in the ACI than in the MF group (1.97 vs 1.57 years). The number of concomitant lesions treated during the study (eg ACL, meniscal lesions, or both)	Eligible patients underwent arthroscopic inspection of the knee and suspected cartilage defect, followed by 1:1 randomised allocation through an IVRS system to either ACI or MF using a minimisation element to achieve treatment balance with respect to surgeon, lesion location, and associated lesions. No details of concealment.	For MRI structural outcome, musculoskeletal radiologists were blinded to treatment allocation.	ACI intervention well detailed. MF intervention not detailed. Outcome measures were the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire, the Visual Analog Scale (VAS) and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) and nine additional items.

		was greater in the MF group.			Adverse events were also reported upon.
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ACI: autologous chondrocyte implantation; AOC: autologous osteochondral cylinder; BMI: body mass index; ICRS: International Cartilage Repair Society; IKDC: International Knee Documentation Committee; IVRS: interactive voice response system; KOOS: Knee injury and Osteoarthritis Outcome Score; LKSS: Lysholm Knee Scoring Scale; MACI: matrix-induced autologous chondrocyte implantation; MF: microfracture; MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue; MRI: magnetic resonance imaging; RCT: randomised controlled trial; SF-36: Short Form-36; VAS: Visual Analog Scale, ... = not reported.

^aThis study has a five year follow-up publication: Knutsen et al, 2007. 'A randomised trial comparing autologous chondrocyte implantation with microfracture, findings at five years', *Journal of Bone and Joint Surgery (American)*, 89, 2105-2112. Some study details obtained from this publication.

^bThis study has a 36 month results publication: Saris et al, 2009. 'Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomised trial compared to microfracture', *American Journal of Sports Medicine*, 37, 10S-19S. Some study details obtained from this publication.

Table 20 Critical appraisal summary of randomised controlled trials: results details

Study	Numbers analysed	Statistical methods	Outcomes and estimation	Ancillary analyses	Adverse events	Follow-up
Level II RCTs						
Basad et al 2010	No power calculations reported. Intention-to-treat analysis not defined. Per-protocol analysis not defined.	Tests detailed: all statistical analyses were performed using the statistics software R version 2.8.0 (2008-10-20) including the Matrix and MASS packages. Significance level detailed: set to $\alpha=5\%$	Results detailed for the Tegner, Lysholm and ICRS scores. No results detailed for 1 week postoperative MRI. Adverse events detailed. Tegner score: median scores provided (no range, mean, SD) Lysholm score: mean and median scores provided, including SD (no range provided). Text describes individual patient scores, but no tabular data provided. ICRS score: individual patient numbers provided (no mean, median, range, SD). Adverse events: discussion of individual incidents only.	No subgroup analyses performed.	Adverse events detailed.	Scheduled follow-up: Patients in both treatment groups were followed up 8-12, 22-26 and 50-54 weeks after surgery. MRI scans were taken 1 week postoperatively. Reported follow-up: By August 2006, 48 patients had completed 2 year follow-up (33 MACI, 15 MF). Losses to follow-up: 4. MF group had 3 losses (1 pregnancy 6 months after treatment, 1 early treatment failure who received OATS after 10 months, 1 discontinued without reason). MACI group had 1 loss (1 discontinued without reason). There were several missing values in both groups due to patients failing to attend for follow-up.
Bentley et al 2003	No power calculations reported. Intention-to-treat analysis not defined. Per-protocol analysis not defined.	Tests detailed: statistical comparison of outcome scores between the groups was performed by the Mann-Whitney U test for non-parametric data. Significance level detailed: a <i>P</i> value <0.05 was taken to be statistically	Results detailed for the Cincinnati rating (authors stated that there was no difference in the results when using either the Cincinnati rating or Stanmore functional rating systems). Number of patients achieving	Subgroup analysis performed for various defect locations: medial femoral condyle, lateral femoral condyle, patella, trochlea, lateral tibial plateau. 37 ACI patients received arthroscopy at one year.	Adverse events detailed.	Scheduled follow-up: Patients underwent regular assessment throughout the postoperative period and at one year. Reported follow-up: Mean follow-up was 19 months (range 12-31).

		significant.	<p>excellent, good, fair or poor results were detailed (no mean, median, range, SD). <i>P</i>-values were provided for differences between ACI and mosaicplasty groups.</p> <p>Results detailed for arthroscopic outcomes.</p> <p>Adverse events: discussion of individual incidents only.</p>	23 mosaicplasty patients received arthroscopy at one year.		Losses to follow-up: none reported.
Dozin et al 2005	<p>60 patients (30 patients each arm) were required to account for the projected rate of recoveries (1/3) occurring during the 6 months elapsing between first (debridement) and second surgery (ACI or mosaicplasty).</p> <p>The authors stated that due to the lower than expected number of patients undergoing either surgical procedure, the study is clearly underpowered to detect clinically meaningful differences between the two procedures.</p> <p>Authors stated that whenever possible, comparisons between the two study groups were based on the intention to treat principle, in that all randomised eligible patients were included and</p>	The outcome was analysed as a categorical variable, with five classes: LKSS<60, LKSS=69 to 90, LKSS >90, subjective improvement, and lost to follow-up. The distribution of patients in these five classes was compared in the two treatment groups by means of the χ^2 for heterogeneity.	Results detailed for the LKSS rating (authors stated that there was no difference in the results when using either the LKSS or Standard IKDC Evaluation Form). Number of patients achieving complete success (>90), partial success (60-90) or failure (<60) were detailed (no mean, median, range, SD). <i>P</i> -values were provided for differences between ACI and mosaicplasty groups.	The study presented results for subjective improvement (group of patients who reported, in a subjective manner, improvement of the symptoms and cure, but could not be subjected to a clinical evaluation) and lost to follow-up (group of patients who did not present at various follow-up examination as scheduled after treatment).	Adverse events not detailed.	<p>Scheduled follow-up: 1, 2, 3, 6, 12, 24, and 36 months postsurgery.</p> <p>Reported follow-up: median 291 days (range 0-1339) in ACI group; median 300 days (range 0-994) in mosaicplasty group.</p> <p>Losses to follow-up: 3 (2 mosaicplasty patients were excluded from the study as their eligibility information was missing; 1 patient refused mosaicplasty and was lost to follow-up).</p> <p>Surgery was accomplished in only 12 of 22 ACI patients and in 11 of 22 mosaicplasty patients. In 14 of these patients this was due to spontaneous improvement in symptoms between first arthroscopic examination/debridement and the scheduled surgery. Two patients refused surgery</p>

	considered in the arm assigned at randomisation, regardless of compliance to the assigned treatment. Per-protocol analysis not defined.					(pregnancy, change of orthopaedic surgeon), and 5 did not show up at the presurgery examination and could not be traced.
Horas et al 2003	No power calculations reported. Authors acknowledged the small number of patients as a limitation of their study. Intention-to-treat analysis not defined. Per-protocol analysis not defined.	The nonparametric Mann-Whitney U test. Because of the repeated measurements in the course of time, the level of significance was corrected according to the Bonferroni method. The level of significance was $P < 0.05$.	Individual scores provided for the Tegner, Lysholm and Meyers outcome scales. Mean scores provided for the ACI and AOC groups (no median, SD, range). P -values were provided for differences between ACI and AOC groups. Adverse events: discussion of individual incidents.	6 ACI patients were re-examined arthroscopically. 3 AOC patients were re-examined arthroscopically.	Adverse events detailed.	Clinical evaluations were performed preoperatively and at 3, 6, 12 and 24 months postoperatively. Losses to follow-up: none reported.
Knutsen et al 2004*	40 patients in each group would be required to demonstrate a difference in the Lysholm and SF-36 scores between the groups of at least 0.75 standard deviations from the mean, with an alpha level of 0.05 and a power level of 90%.	t tests, the Pearson chi-square and Mann-Whitney U tests, and multiple linear regression models were used. The level of significance was $P < 0.05$.	Box plot used to report Lysholm, SF-36 and visual analog scale scores, with median scores also marked on each box. P -values were provided for differences between ACI and microfracture groups.	Clinical data on the patients who did not have a failure were collected at 2 and 5 years. Subgroup analysis conducted for younger (<30 years old) patients vs older patients. Sub-group analysis conducted for histological quality of biopsy specimens from 12 patients with a failure versus 55 patients without a failure.	Adverse events detailed.	Two years and five years. Losses to follow-up: at 5 years no patient had been lost to follow-up.
Saris et al 2008	The sample size for this study was determined using a categorisation (success/failure) whereby the presence of hyaline or hyaline-like tissue was	In the case of treatment failure a LOCF approach was used to impute missing scores corresponding to visits the patient would already have	KOOS: mean scores provided (\pm SE), and t values were provided. P -values were provided for significant differences between ACI and MF	KOOS subgroup analyses were performed: Patients with symptom onset of <2 versus >2 years	Adverse events detailed.	6, 12, 18 and 36 months postoperative. Losses to follow-up: ACI group 16, MF group 17.

	<p>recorded as a success and fibrocartilage or noncartilage as a failure. It was assumed that 30% of patients allocated to MF would be categorised as a success and that an improvement in this success rate to 60% success with CCI would constitute a clinically significant improvement. On this basis, with 90% power and using a 2.5% one-sided test, it was calculated that a total enrolment of 112 patients (56/group) would be required.</p>	<p>reached had they not failed. The long-term clinical superiority of ACI over MF was also tested using a prespecified mixed linear model. A heterogeneous compound symmetry (CSH) structure and an unstructured variance-covariance structure were considered. The degree of knee disorder severity was compared using the Cochran-Armitage test for trend, and comparison of responder status was performed using an χ^2 test. The Kaplan-Meier product limit estimator was used to display time to treatment failure for each treatment group and compared by the log-rank test. The Fisher exact test was used for between-group differences for AEs with a frequency of >5%. For MRI assessments, point estimates of treatment differences, associated 95% confidence intervals, and probability values were analysed using similar covariance models and approaches previously described.</p> <p>Significance level not defined.</p>	<p>groups.</p> <p>MRI structural outcome: mean absolute values provided. <i>P</i>-values were provided for significant differences between ACI and MF groups.</p> <p>Adverse events: discussion of individual incidents.</p>	<p>ACI patients with high (≥ 2) compared with low (< 2) CC scores.</p>		
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ACI: autologous chondrocyte implantation; AOC: autologous osteochondral cylinder; AEs: adverse events; CCI: characterised chondrocyte implantation; ICRS: International Cartilage Repair Society; IKDC: International Knee Documentation Committee; KOOS: Knee injury and Osteoarthritis Outcome Score; LKSS: Lysholm Knee Scoring Scale; MACI: matrix-induced autologous chondrocyte implantation; MF: microfracture; MRI: magnetic resonance imaging; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form-36; ... = not reported.

^aThis study has a five year follow-up publication: Knutsen et al, 2007. 'A randomised trial comparing autologous chondrocyte implantation with microfracture, findings at five years', *Journal of Bone and Joint Surgery (American)*, 89, 2105-2112. Some study details obtained from this publication

^bThis study has a 36 month results publication: Saris et al, 2009., 'Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomised trial compared to microfracture', *American Journal of Sports Medicine*, 37, 10S-19S. Some study details obtained from this publication.

Appendix E Studies included in the review

Systematic reviews and health technology assessments

- Brittberg M, 2010. 'Cell carriers as the next generation of cell therapy for cartilage repair: A review of the matrix-induced autologous chondrocyte implantation procedure', *American Journal of Sports Medicine*, 38 (6), 1259-1271.
- Clar C, Cummins E, et al, 2005. 'Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: Systematic review and economic evaluation', *Health Technology Assessment*, 9 (47), iii-iv, ix-x, 1-82.
- Jobanputra P, Parry D, et al, 2001. 'Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: A rapid and systematic review', *Health Technology Assessment*, 5 (11), 1-57.
- Kon E, Verdonk P, et al, 2009. 'Matrix-assisted autologous chondrocyte transplantation for the repair of cartilage defects of the knee: Systematic clinical data review and study quality analysis', *American Journal of Sports Medicine*, 37 (Suppl 1), 156S-166S.
- Kunzl M, Mathis S and Johansson T, 2009. 'Autologous chondrocyte implantation systematic review', *HTAProjektbericht (Ludwig Boltzmann Institut für Health Technology Assessment)*, Number 34.
- Magnussen RA, Dunn WR, et al, 2008. 'Treatment of focal articular cartilage defects in the knee: A systematic review', *Clinical Orthopaedics and Related Research*, 466 (4), 952-962.
- Ruano-Ravina A and Jato Díaz M, 2005. 'Autologous chondrocyte implantation: A systematic review', *Osteoarthritis and Cartilage*, 14 (1), 47-51.
- Vasiliadis HS, Wasiak J and Salanti G, 2010. 'Autologous chondrocyte implantation for the treatment of cartilage lesions of the knee: A systematic review of randomized studies', *Knee Surgery, Sports Traumatology, Arthroscopy*, Feb 2 [Epub ahead of print].
- Wasiak J, Clar C and Villanueva E, 2007. 'Autologous cartilage implantation for full thickness articular cartilage defects of the knee', *Cochrane Database of Systematic Reviews*, Issue 3.
- Zengerink M, Struijs PA, et al, 2010. 'Treatment of osteochondral lesions of the talus: a systematic review', *Knee Surgery, Sports Traumatology, Arthroscopy*, 18 (2), 238-246.

Studies included for safety

Comparative studies

- Basad E, Ishaque B, et al, 2010. 'Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study', *Knee Surgery, Sports Traumatology, Arthroscopy*, Jan 9 [Epub ahead of print].

- Bentley G, Biant LC, et al, 2003. 'A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee', *Journal of Bone and Joint Surgery (British)*, 85 (2), 223-230.
- Derrett S, Stokes EA, et al, 2005. 'Cost and health status analysis after autologous chondrocyte implantation and mosaicplasty: a retrospective comparison', *International Journal of Technology Assessment in Health Care*, 21 (3), 359-367.
- Fu FH, Zurakowski D, et al, 2005. 'Autologous chondrocyte implantation versus debridement for treatment of full-thickness chondral defects of the knee: an observational cohort study with 3-year follow-up', *American Journal of Sports Medicine*, 33 (11), 1658-1666.
- Horas U, Pelinkovic D, et al, 2003. 'Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial', *Journal of Bone and Joint Surgery (American)*, 85-A (2), 185-192.
- Knutsen G, Engebretsen L, et al, 2004. 'Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial', *Journal of Bone and Joint Surgery (American)*, 86-A (3), 455-464.

Follow-up publication:

- Knutsen G, Drogset JO, et al, 2007. 'A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years', *Journal of Bone and Joint Surgery (American)*, 89 (10), 2105-2112.
- Kon E, Gobbi A, et al, 2009. 'Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years', *American Journal of Sports Medicine*, 37 (1), 33-41.
- Salzmann GM, Paul J, et al, 2009. 'T2 assessment and clinical outcome following autologous matrix-assisted chondrocyte and osteochondral autograft transplantation', *Osteoarthritis and Cartilage*, 17 (12), 1576-1582.
- Saris DB, Vanlauwe J, et al, 2008. 'Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture', *American Journal of Sports Medicine*, 36 (2), 235-246.

36-month results also included:

- Saris DB, Vanlauwe J, et al, 2009. 'Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture', *American Journal of Sports Medicine*, 37 (Suppl 1), 10S-19S.
- Welsch GH, Mamisch TC, et al, 2008a. 'Cartilage T2 assessment at 3-T MR imaging: in vivo differentiation of normal hyaline cartilage from reparative tissue after two cartilage repair procedures--initial experience', *Radiology*, 247 (1), 154-161.

Comparative studies treated as case series

- Erggelet C, Kreuz PC, et al, 2009. 'Autologous chondrocyte implantation versus ACI using 3D-bioresorbable graft for the treatment of large full-thickness cartilage lesions of the knee', *Archives of Orthopaedic and Trauma Surgery*, Aug 27 [Epub ahead of print].
- Ferruzzi A, Buda R, et al, 2008. 'Autologous chondrocyte implantation in the knee joint: open compared with arthroscopic technique. Comparison at a minimum follow-up of five years', *Journal of Bone and Joint Surgery (American)*, 90 (Suppl 4), 90-101.
- Steinwachs M and Kreuz PC, 2007. 'Autologous chondrocyte implantation in chondral defects of the knee with a type I/III collagen membrane: a prospective study with a 3-year follow-up', *Arthroscopy*, 23 (4), 381-387.
- Wondrasch B, Zak L, et al, 2009. 'Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle on radiographic and clinical outcome after 2 years: a prospective, randomized controlled pilot study', *American Journal of Sports Medicine*, 37 (Suppl 1), 88S-96S.

Case series

- Baums MH, Heidrich G, et al, 2006. 'Autologous chondrocyte transplantation for treating cartilage defects of the talus', *Journal of Bone and Joint Surgery (American)*, 88 (2), 303-308.
- Brittberg M, Lindahl A, et al, 1994. 'Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation', *New England Journal of Medicine*, 331 (14), 889-895.
- Browne JE, Anderson AF, et al, 2005. 'Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects', *Clinical Orthopaedics and Related Research*, 436, 237-245.
- Cherubino P, Grassi FA, et al, 2003. 'Autologous chondrocyte implantation using a bilayer collagen membrane: a preliminary report', *Journal of Orthopaedic Surgery (Hong Kong)*, 11 (1), 10-15.
- Farr J, 2007. 'Autologous chondrocyte implantation improves patellofemoral cartilage treatment outcomes', *Clinical Orthopaedics and Related Research*, 463, 187-194.
- Ferruzzi A, Calderoni P, et al, 2004. 'Autologous chondrocytes implantation: indications and results in the treatment of articular cartilage lesions of the knee', *La Chirurgia degli Organi di Movimento*, 89 (2), 125-134.
- Giannini S, Buda R, et al, 2008. 'Arthroscopic autologous chondrocyte implantation in osteochondral lesions of the talus: surgical technique and results', *American Journal of Sports Medicine*, 36 (5), 873-880.
- Giannini S, Buda R, et al, 2005. 'The detached osteochondral fragment as a source of cells for autologous chondrocyte implantation (ACI) in the ankle joint', *Osteoarthritis and Cartilage*, 13 (7), 601-607.

- Giannini S, Battaglia M, et al, 2009. 'Surgical treatment of osteochondral lesions of the talus by open-field autologous chondrocyte implantation: a 10-year follow-up clinical and magnetic resonance imaging T2-mapping evaluation', *American Journal of Sports Medicine*, 37 (Suppl 1), 112S-118S.
- Gobbi A, Kon E, et al, 2009. 'Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation: results at 5 years' follow-up', *American Journal of Sports Medicine*, 37 (6), 1083-1092.
- Gobbi A, Kon E, et al, 2006. 'Patellofemoral full-thickness chondral defects treated with hyalograft-C: A clinical, arthroscopic, and histologic review', *American Journal of Sports Medicine*, 34 (11), 1763-1773.
- Haddo O, Mahroof S, et al, 2004. 'The use of chondroide membrane in autologous chondrocyte implantation', *Knee*, 11 (1), 51-55.
- Halbrecht JL and Klick BC, 2006. 'Improvement in bone homeostasis following autologous chondrocyte implantation of the knee', *Orthopedics*, 29 (1), 61-69.
- Koulalis D, Schultz W, et al, 2004. 'Articular reconstruction of osteochondral defects of the talus through autologous chondrocyte transplantation', *Orthopedics*, 27 (6), 559-561.
- Kreuz PC, Muller S, et al, 2009. 'Treatment of focal degenerative cartilage defects with polymer-based autologous chondrocyte grafts: Four-year clinical results', *Arthritis Research and Therapy*, 11 (2), R33, Epub 2009 Mar 5.
- Kreuz PC, Steinwachs M, et al, 2007. 'Classification of graft hypertrophy after autologous chondrocyte implantation of full-thickness chondral defects in the knee', *Osteoarthritis and Cartilage*, 15 (12), 1339-1347.
- Krishnan SP, Skinner JA, et al, 2006. 'Collagen-covered autologous chondrocyte implantation for osteochondritis dissecans of the knee: two- to seven-year results', *Journal of Bone and Joint Surgery (British)*, 88 (2), 203-205.
- Løken S, Ludvigsen TC, et al, 2009. 'Autologous chondrocyte implantation to repair knee cartilage injury: ultrastructural evaluation at 2 years and long-term follow-up including muscle strength measurements', *Knee Surgery, Sports Traumatology, Arthroscopy*, 17 (11), 1278-1288.
- Mandelbaum B, Browne JE, et al, 2007. 'Treatment outcomes of autologous chondrocyte implantation for full-thickness articular cartilage defects of the trochlea', *American Journal of Sports Medicine*, 35 (6), 915-921.
- Marcacci M, Kon E, et al, 2007. 'Arthroscopic second generation autologous chondrocyte implantation', *Knee Surgery, Sports Traumatology, Arthroscopy*, 15 (5), 610-619.
- Marlovits S, Striessnig G, et al, 2005. 'Early postoperative adherence of matrix-induced autologous chondrocyte implantation for the treatment of full-thickness cartilage defects of the femoral condyle', *Knee Surgery, Sports Traumatology, Arthroscopy*, 13 (6), 451-457.

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- Micheli LJ, Moseley JB, et al, 2006. 'Articular cartilage defects of the distal femur in children and adolescents: treatment with autologous chondrocyte implantation', *Journal of Pediatric Orthopedics*, 26 (4), 455-460.
- Minas T, 2001. 'Autologous chondrocyte implantation for focal chondral defects of the knee', *Clinical Orthopaedics and Related Research*, 391 (Suppl), S349-S361.
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- Mithöfer K, Peterson L, et al, 2005. 'Articular cartilage repair in soccer players with autologous chondrocyte transplantation: functional outcome and return to competition', *American Journal of Sports Medicine*, 33 (11), 1639-1646.
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- Peterson L, 1998. 'Long-term clinical results of using autologous chondrocytes to treat full-thickness chondral defects', *Journal of Sports Traumatology and Related Research*, 20 (2), 103-108.
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- Robertson WB, Fick D, et al, 2007. 'MRI and clinical evaluation of collagen-covered autologous chondrocyte implantation (CACI) at two years', *Knee*, 14 (2), 117-127.

- Rogers BA, David LA and Briggs TW, 2009. 'Sequential outcome following autologous chondrocyte implantation of the knee: A six-year follow-up', *International Orthopaedics*, Aug 11 [Epub ahead of print].
- Rosenberger RE, Gomoll AH, et al, 2008. 'Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older', *American Journal of Sports Medicine*, 36 (12), 2336-2344.
- Schneider TE and Karaikudi S, 2009. 'Matrix-Induced Autologous Chondrocyte Implantation (MACI) grafting for osteochondral lesions of the talus', *Foot and Ankle International*, 30 (9), 810-814.
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Studies included for effectiveness

Comparative studies

- Basad E, Ishaque B, et al, 2010. 'Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study', *Knee Surgery, Sports Traumatology, Arthroscopy*, Jan 9 [Epub ahead of print].
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- Dozin B, Malpeli M, et al, 2005. 'Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial', *Clinical Journal of Sport Medicine*, 15 (4), 220-226.
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Knutsen G, Engebretsen L, et al, 2004. 'Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial', *Journal of Bone and Joint Surgery (American)*, 86-A (3), 455-464.

Follow-up publication:

Knutsen G, Drogset JO, et al, 2007. 'A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years', *Journal of Bone and Joint Surgery (American)*, 89 (10), 2105-2112.

Kon E, Gobbi A, et al, 2009. 'Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years', *American Journal of Sports Medicine*, 37 (1), 33-41.

Salzmann GM, Paul J, et al, 2009. 'T2 assessment and clinical outcome following autologous matrix-assisted chondrocyte and osteochondral autograft transplantation', *Osteoarthritis and Cartilage*, 17 (12), 1576-1582.

Saris DB, Vanlauwe J, et al, 2008. 'Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture', *American Journal of Sports Medicine*, 36 (2), 235-246.

36-month results also included:

Saris DB, Vanlauwe J, et al, 2009. 'Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture', *American Journal of Sports Medicine*, 37 (Suppl 1), 10S-19S.

Trattinig S, Mamisch TC, et al, 2008. 'Differentiating normal hyaline cartilage from post-surgical repair tissue using fast gradient echo imaging in delayed gadolinium-enhanced MRI (dGEMRIC) at 3 Tesla', *European Radiology*, 18 (6), 1251-1259.

Welsch GH, Mamisch TC, et al, 2008a. 'Cartilage T2 assessment at 3-T MR imaging: in vivo differentiation of normal hyaline cartilage from reparative tissue after two cartilage repair procedures--initial experience', *Radiology*, 247 (1), 154-161.

Welsch GH, Trattinig S, et al, 2008b. 'Magnetization transfer contrast and T2 mapping in the evaluation of cartilage repair tissue with 3T MRI', *Journal of Magnetic Resonance Imaging*, 28 (4), 979-986.

Welsch GH, Trattinig S, et al, 2009. 'Multimodal approach in the use of clinical scoring, morphological MRI and biochemical T2-mapping and diffusion-weighted imaging in their ability to assess differences between cartilage repair tissue after microfracture therapy and matrix-associated autologous chondrocyte transplantation: a pilot study', *Osteoarthritis and Cartilage*, 17 (9), 1219-1227.

Appendix F Studies providing level IV safety data

Table 21 Characteristics of studies providing level IV safety evidence

Study (study period)	Patient allocation	No. of patients (knees)	Age (years) Mean \pm SD	Male / Female	Length of follow-up	Lost to follow-up
Brittberg et al 1994 (...)	...	23 (23)	27 \pm 8.4 (range: 14–48)	11/12	Mean 39 \pm 13.5 months (range: 16–66)	...
Browne et al 2005 (March 1995–May 1996)	Prospective, consecutive	100 (100)	37.0 \pm 9.1 (range: 14–55)	65/35	Planned: 5 years	13
Cherubino et al 2003 (December 1999–January 2001)	...	13 (13)	35 (range: 18–49)	9/4	Mean 6.5 (range: 2–15) months	0
Erggelet et al 2009 ^a (March 1997–October 2004)	Retrospective	<i>Periosteum ACI</i> 42 (...)	34 (range: 16–53)	28/14	36 months (range: 24–63)	0
		<i>BioSeed-C ACI</i> 40 (...)	36 (range: 17–63)	22/18	24 months	3
Farr 2007 (September 1998–November 2005)	Prospective	38 (39)	31.2 \pm 11.3 (range: 14.9–50.5)	21/17	Median 3.1 years (range: 0.5–5.1 years)	... (1 patient had missing data and 3 patients had data collected at earlier times. Their 2-year follow-up scores were carried forward from their last observation)
Ferruzzi et al 2008 (1997–2002) ^a	...	<i>Open ACI</i> 48 (...)	32.1	30/18	6, 12, 18, and 24 months, then yearly	...
		<i>Arthroscopic ACI</i> 50 (...)	31.0	36/14		
Ferruzzi et al 2004 (1997–2000)	...	40 (...)	36.1 (range: 18–55)	24/16	Planned: 3, 6, 12, 18, 24 months	...
Gobbi et al 2006 and Gobbi et al 2009 ^b (September 1999–	Consecutive	34 (34)	31.2 (range: 15–55)	23/11	Planned: 12, 24 and 60 months Mean 75.5 months	4

January 2003)					(range: 60–105)	
Haddo et al 2004 (Recruitment: July 1998–August 2001)	...	31 (33) ^c	31 (range: 15–51)	20/10	Planned: 12, 24 months Mean actual: 12.6 and 23 months	At time of report, 15 questionnaires complete (2 yr), 32 knees reviewed clinically (1 yr), 33 defects reviewed arthroscopically (1 yr)
Halbrecht et al 2006 (September 1995–June 2001)	...	31 (34 implants) ^d	39.1 (range: 17–54)	16/8	Mean \pm SEM: 26.5 \pm 3.5 months	7
Kreuz et al 2009 (December 2001–October 2002)	Prospective	19 (...)	35 (range: 25–50)	11/8	Planned: 0, 6, 12, and 48 to 60 months	2
Kreuz et al 2007 (1996–2000)	...	102 (102)	34 \pm 8.8	63/39	Planned: 6, 8, 36 months	0
Krishnan et al 2006 (1998–2003)	Prospective	37 (...)	Juvenile-onset OD: 23.8 (range: 15–36) Adult-onset OD: 40 (range: 36–44)	23/14	Mean 4.08 \pm 1.2 years (range: 2–7)	...
Loken et al 2009 (1997–1999)	Prospective, consecutive	21 (...)	289 (range: 16–45)	12/9	1, 2 and 8.1 years	3
Mandelbaum et al 2007 (...)	Prospective	40 (...)	37 \pm 8.5 (range: 16–48)	28/12	Mean 59 \pm 18 months (range: 24–84)	0
Marcacci et al 2007 (...)	Prospective, consecutive	70 (70)	29 (range: 16–60)	...	12, 24, 36 (only 47 patients), 48 (only 21 patients) months	36 months (23) 48 months (49)
Marvolits et al 2005 (...)	Prospective	16 (16)	33.1 \pm 7.1 (SEM) (range: 20.1–44.3)	15/1	Mean 34.7 days (range: 22–47)	0
Micheli et al 2001 (March 1995–December 1996)	Prospective, consecutive	50 (50)	36 \pm 8	37/13	Minimum 36 months	...

Micheli et al 2006 (1995–2000)	Prospective	37 (...)	15.5 ± 1.6 (range: 11–17)	22/15	Mean 4.3 years	5
Minas et al 2001 (March 1995–December 1999)	Prospective	169 (...)	Simple group: mean 35 Complex group: mean 35 Salvage group: mean 39 (range 13–58)	116/53	Planned: 12, 18 and 24 months Actual: ... (results only recorded for patients with minimum 12 month follow-up)	62 lost at >12 months, 113 lost at > 24 months
Mithofer et al 2005 (December 1995–December 2000)	Prospective	20 patients with 29 lesions (23)	15.9 ± 0.3 (range: 12–18)	15/5	Mean 47 ± 4 months (range: 23-91)	...
Mithofer et al 2005 (March 1998–August 2000)	Prospective, consecutive	45 (...)	26 ± 1 (range: 14–43)	32/13	41 ± 4 (range: 12-108) months	2
Nehrer et al 2006 (December 2001–September 2004)	Prospective	36 (...)	33 ± 11.8 (range: 14–54)	19/17	Planned: 6, 12, 24, and 36 months	...
Niemeyer et al 2008 (2001–2006)	Consecutive	309 patients underwent 349 ACI procedures (...)	35.2 ± 9.2	165/144	For all ACI patients: ... For patients with ACI revision: mean 4.5 ± 1.5 years	For all ACI patients: ... For patients with ACI revision: 4
Ossendorf et al 2007 (March 1997–December 2001)	Prospective, consecutive	71 with 73 defects (71)	35 (range: 13–61)	47/24	Mean 3 years (range: 24-65 months)	...
Pascual-Garrido et al 2009 (January 2002–December 2006)	Prospective, consecutive	62 (63)	31.8 ± 8.6 (range: 15.8–49.4)	26/26	Mean 4 years (range: 2-7)	...
Perez-Cachafeiro et al 2010 (April 2001–January)	Prospective, consecutive	111 (...)	30.9 (95% CI: 29.1–32.7)	80/31	Planned: 15 days, 1.5, 3, 6, 12, 24, 36, 48, 60 months	% of analysed patients at follow-up: 15 days: 47.3% 1.5 months: 73.6% 3 months: 89.1%

2005)						6 months: 87.3% 12 months: 83.6% 24 months: 64.5% 36 months: 62.2% 48 months: 16.9% 60 months: 24%
Peterson 1998 (October 1987–October 1997)	Consecutive	92 (...)	Isolated femoral condyle group: 4.1 years Femoral condyle-ACL group: 3.8 years Osteochondritis dissecans: 3.9 years Patella: NR Femoral condyle and other lesions: NR	...
Peterson et al 2003 (1990–April 2000)	...	58 (...)	26.4 (range: 14–52)	30/28	Mean 5.6 years (range: 1-10)	...
Pietschmann et al 2009 (...)	Consecutive	30 (30)	33.2 (range: 15.3–49.8)	19/11	Planned: 6, 12 months	2 ^e
Robertson et al 2007 (March 1999–June 2001)	...	31 (...)	37.4 (range: 19–60)	...	Planned: 3, 6, 12, 24 months	1
Rogers et al 2009 (July 1998–...)	Prospective, consecutive	57 (...)	31.6 (range: 15–51)	31/26	Planned: 6 years	...
Rosenberger et al 2008 (...)	Prospective	56 (...)	48.6 (range: 45–60)	36/20	Mean 54.6 months (range 24–135)	2
Steinwachs et al 2007 ^a (2000-2002)	Prospective, consecutive	63 (...)	34.3 (range: 18-50)	31/32	6, 18 and 36 months	...
Wondrasch et al 2009 ^a (...)	Prospective, consecutive	31 (31)	33 (range: 18-55)	23/8	4, 12, 24, 52, and 104 weeks	0
Wood et al 2006	...	294 (...)	Median 38 (range: 13–60)	185/109

(1996–2003)						
Yates 2003 (1995–1999)	Prospective	24 (24)	23.8 (range: 25–52)	19/5	Planned: 6, 12 months Actual: 18 patients had a minimum of 12 months follow-up	1 (deceased)

ACI: autologous chondrocyte implantation; CI: confidence interval; OD: osteochondritis dissecans; SD: standard deviation; SEM: standard error of mean; ... = not reported

^acomparative studies treated as case series

^bGobbi et al 2006 and Gobbi et al 2009 report on the same patient population. Gobbi et al 2009 reports on an additional two patients than Gobbi et al 2006 while Gobbi et al 2006 reports an additional adverse event (fibrosis in one patient) not reported by Gobbi et al 2006. Study characteristics are for Gobbi et al 2009

^cone patient awaiting one year arthroscopy excluded

^dthe data presented covers only 24 evaluated patients

^ethese two patients reported as lost to follow-up, however they represented treatment failures and have been included in the safety table below

Table 22 Adverse events reported in studies providing level IV safety evidence

Study	Flap/matrix type	No. of patients (knees)	Adverse events (number of events) (resolution of adverse event, where reported)	Total adverse events
Brittberg et al 1994	Periosteum	23 (23)	Loosening of the condylar transplant (1) (solved by suturing of the transplant to surrounding articular cartilage 6 months after initial surgery, subsequent removal of 1/3 of the transplant 10 months later due to ongoing transplant looseness and locking of the knee) Severe central wear resulting in locking of the knee and pain (2) (degenerative tissue debrided and resurfaced with subchondral drill holed filled with carbon-fibre implants) Knee infections (0) Severe chondromalacia (2) (required debridement and surgical resection of the failed graft and subchondral bone combined with the implantation of carbon-fibre pads at 16 or 24 months after transplantation).	5
Browne et al 2005	Periosteum	100 (100)	Joint infection (0) Arterial injury (0) Nerve injury (0) DVT in non-operated limb (1) (resolved with anticoagulants) Reflex sympathetic dystrophy (2) Limited range of motion (2) (both required closed manipulation under anaesthesia, 1 resolved without sequelae and the other required a subsequent arthroscopy for lysis of adhesions) Subsequent operations after treatment failure (12) (surgeries included 3 total knee replacements, 2 reimplantations, 1 reimplantation twice, 2 marrow stimulation technique procedure, 2 debridement of the original implant site, 1 osteochondral autograft transplantation) Subsequent arthroscopic operations in patients without treatment failure (24) (findings included 6 adhesions; 5 hypertrophic changes of the graft; 4 loose bodies; 4 loose, delaminated, and/or partially delaminated periosteal patch; and 4 meniscal tears) Subsequent non-arthroscopic operation in patients without treatment failure (1) (1 tibial cyst excision)	42
Cherubino et al 2003	Bilayer type I-III collagen membrane	13 (13)	No complications were observed in the postoperative period	0
Erggelet et al 2009 ^a	Periosteum and BioSeed-C	82 (...)	Joint infection (0) Allergic reaction (0) Extension lag (0) Flexion deficit (0) Moderate effusion (1) (no other problems, and did well later on) Treatment failure (1) (due to soft regeneration tissue after 9 months, graft removed) Revision surgery (15) (1 graft removal, 2 synovectomies, 1 debridement, 1 total knee replacement) Symptomatic periosteal hypertrophy (4) Graft failure (4) Plica syndrome (2)	28

			Synovectomy (1)	
Farr 2007	Periosteum	38 (39)	Subsequent operation after ACI due to pain resulting from osteotomy hardware, minor patellofemoral symptoms such as crepitus, mild pain or catching (14) Subsequent operation after ACI due to major mechanical symptoms such as marked catching or clunking – presumed due to periosteal patch overgrowth, periosteal patch delamination or focal scar tissue (7) (2 were treatment failures which were treated with microfracture) Ossification of the graft in 12 patients with graft or periosteal patch hypertrophy (0) Limited range of motion (5) (required subsequent operation due to postoperative scar impingement or presence of some degree of arthrofibrosis – none had patellar infera) Subsequent operation after ACI due to substantial patellofemoral pain (3) (a cartilage lesion ICRS Grade 1B-2 was the only finding at arthroscopy) Acute knee sepsis (1) (implants were removed and patient was a treatment failure) Subsequent operation to remove hardware for an unrelated femur fracture treated before implantation (1) Medial meniscal tear (1) (underwent arthroscopy with partial meniscectomy)	32
Ferruzzi et al 2008 ^a	Hyaluronic acid 3D scaffold (Hyaff-11)	98 (...)	Graft hypertrophy (6) (all underwent surgical debridement of graft 12 months after surgery) Delaminations (2) (all underwent surgical debridement of graft 12 months after surgery) Treatment failure (2) (arthroscopic shaving performed 12 months after surgery) Graft hypertrophy with loose bodies (1) (...)	11
Ferruzzi et al 2004	Periosteum	40 (...)	Early (not defined) haemarthrosis (1) (solved by rest and ice) Early (not defined) joint stiffness (1) (required mobilisation in narcosis) Hypertrophy of repair tissue at mean 6 months after implantation (3) (arthroscopic shaving with resolution of symptoms)	5
Gobbi et al 2006 and Gobbi et al 2009 ^b	Hyalograft C	34 (34)	Fibrosis (1) (resolved with another arthroscopy to release fibrotic scar tissues) Mechanical symptoms (4) (required second-look arthroscopy) Requirement for second-look arthroscopy (patients with pain or requiring surgical treatment on same knee for unrelated causes) (4) (...)	9
Haddo et al 2004 ^c	Chondrogide	31 (33)	Hypertrophy (1) (...)	1
Halbrecht et al 2006 ^d	Periosteum	31 (34 implants)	Periosteal hypertrophy (3) (resolved with arthroscopic shaving) Intra-articular adhesions (3) (resolved with arthroscopic lysis of adhesions) Signs of early cellulites (1) (successfully treated with antibiotics)	7
Kreuz et al 2009	BioSeed-C	19 (...)	Persistent knee joint infection (0) Allergic reactions (0) Knee joint effusion/swelling (9) (...) Symptoms of temporary blocking (4) (...) Graft-related autoimmune disorders (0) Signs of hypersensitivity (0) Malignant transformation (0) Migration of chondrocytes (0) Poisoning (0) Toxicity (0) Organ failure (0)	24

			<p>Hepatic or renal disorders (0) Reproductive defects (0) Teratogenic effects (0) Second-look arthroscopy due to symptoms like persistent grinding, catching, pain or swelling (9) (...) Persistent pain and failure of ACI procedure, requiring total knee endoprosthesis 4 years after graft implantation (2) (...)</p>	
Kreuz et al 2007 ^e	Periosteum	102 (102)	<p>(≤ 150%) hypertrophy at 6 months (11) (no further surgical intervention) Grade 3 (≤ 200%) hypertrophy at 6 months (8) (6 treated with arthroscopic shaving; in 2 patients hypertrophic area trimmed down and microfracture performed in region without integration to surrounding cartilage) Grade 4 (> 200%) hypertrophy at 6 months (4) (2 underwent arthroscopic shaving, 2 underwent second ACI) Grade 2 hypertrophy at 36 months (5) (...)</p>	28
Krishnan et al 2006	Porcine collagen membrane	37 (...)	<p>Knee stiffness (1) (improved after manipulation under anaesthesia) Unexplained graft failure at 4 years (1) (treated by revision ACI-C)</p>	2
Loken et al 2009	Periosteum	21 (...)	<p>Cerebral insult during ACI operation (1) (patient's overall general health has been markedly impaired after this episode) Acute loosening of the transplant from the trochlea (1) (treatment failure, patient treated with osteochondral cylinder transfer) Treatment failure (2) (one patient treated with unicondylar knee prostheses after 43 months and one patient treated with microfracture after 22 months) Subsequent re-arthroscopy for pain or mechanical symptoms (5)</p>	9
Mandelbaum et al 2007	Periosteum	40 (...)	<p>Subsequent arthroscopic procedures (17) Reasons for/findings at subsequent procedures: Adhesions (4) Periosteal flap detachment (4) Chondromalacia (4) Loose bodies (3) Torn meniscus (3) Fibrotic tissue (2) Decreased range of motion (2) Chondromalacia observed in subsequent surgeries (4) (assessed by the treating surgeon as related to ACI in 1 case, not related in 2 cases and unspecified in 1 case) Failures (0)</p>	23
Marcacci et al 2007	Hyalograft-C	70 (70)	<p>No complications related to the implant or serious adverse events were observed during the treatment and follow-up period</p>	0
Marvolits et al 2005	3-D Collagen Type I-III membrane	16 (16)	<p>In the early postoperative period, no infections or further complications were observed</p>	0
Micheli et al 2001 ^f	Periosteum	50 (50)	<p>Hypertrophy of the periosteal patch (6) (5 recovered without the need for further intervention, 1 developed second lesion in the same knee and underwent reimplantation with cultured chondrocytes)</p>	12

			Adhesions (3) (the 3 patients underwent arthroscopic treatment for lysis of adhesions and subsequently recovered without additional complications) Graft failure (3) (all required reimplantation or other cartilage repair techniques)	
Micheli et al 2006	Periosteum	37 (...)	Patella mal-tracking (1) Clicking/popping (1) Periosteal patch displacement (1) Scar tissue (1) Hypertrophy of graft (2) Severe pain in the treated knee 2 months post ACI (1) Partial graft delamination (1)	8
Minas et al 2001	Periosteum	169 (...)	Need for second look arthroscopy (42) (8 for arthrofibrosis and 34 for periosteal hypertrophy) Failure of revision ACI and progressive degeneration (1) (patient required a total knee replacement) Treatment failure (22) (due to poor integration or quality (soft fibrous graft) or graft delamination in 13 patients, noncompliant rehabilitation in 2 patients, traumatic event after implantation in 4 patients and progressive degenerative disease in 3 patients; 8 patients underwent successful revision ACI, 1 underwent patellectomy, 1 underwent cadaveric allograft replacement, 2 had total knee replacements, and 9 underwent arthroscopic debridement alone and did not want additional treatment)	65
Mithofer et al 2005	Periosteum	20 patients with 29 lesions (23)	Graft hypertrophy (3) (successfully treated with arthroscopic chondroplasty in all cases)	3
Mithofer et al 2005	Periosteum	45 (...)	Failure of repair (6) (all treated with revision ACI, 3/6 (50%) resulted in a good or excellent clinical rating) Graft delamination (3) (...)	9
Nehrer et al 2006	Hyalograft-C	36 (...)	<i>Immediate postoperative period</i> Moderate fever (<38°C) (3) (symptoms resolved within 3 days and no additional treatment was necessary) Concomitant effusion (2) (symptoms resolved within 3 days and no additional treatment was necessary) There were no severe adverse events observed	5
Niemeyer et al 2008	Periosteum n=52 Chondrogide n=215 Three-dimensional matrix-associated procedure (BioSeed-C) n=82	309 patients underwent 349 ACI procedures (...)	Required revision surgery (52) (14 had received periosteum-covered ACI, 26 had received Chondrogide-covered ACI, 12 had received matrix-associated (BioSeed-C) ACI). Intraoperative pathologic findings for the 52 patients requiring revision included: hypertrophy of the regenerated cartilage (16), insufficient fusion between the regenerated cartilage and healthy cartilage at the edge of the former defect (12), insufficient or incomplete regenerative cartilage (9), delamination of intact cartilage in the range of the defect (9), traumatic cartilage lesion in the area of the ACI (1) (due to an accident), arthrofibrosis (3) (treated with arthroscopic arthrolysis), osteonecrosis of the subchondral bone in the defect area (2) (both treated with anterograde drilling)	52
Ossendorf et al 2007	Periosteum	71 patients with 73 defects (...)	Joint infection (0) Flexion deficit (0) Extension deficit (0) Effusion of clinical relevance (0)	12

			Revision surgery (12) (8 due to ACI complications: graft failure (3), hypertrophy (3), delaminating of the periosteal flap (2); 4 due to locking sensations caused by plica synovialis (1) and osteochondrosis dissecans (2), and one patient's graft was removed in another hospital at the patient's request)	
Pascual-Garrido et al 2009	Periosteum	62 (63)	Subsequent surgical procedures (23) Reasons for subsequent procedures: Periosteal graft hypertrophy (13) Painful hardware necessitating removal (2) New cartilage lesion in the femoral condyle (treated successfully with a microfracture procedure (2) Loose body removal with concomitant microfracture of the medial and lateral femoral condyle after a traumatic event (1) Cartilage loss in the previous trochlea ACI area with a concomitant new medial femoral condyle lesion (1) Clinical failure and conversion to total knee replacement (2) Failure converted to an osteochondral allograft (ACI with AMZ group) (1) Failure converted to an osteochondral allograft (failed AMZ with subsequent ACI) (1)	23
Perez-Cachafeiro et al 2010	Periosteum	111 (...)	12 months (treatment necessary for 18 of 19 these adverse events with additional surgery required in 8): joint effusions (9) infections (4) blockages (3) patellar malalignment (1) displaced grafts (1) adhesions (1) 24 months: mild to moderate pain (2) (...) 36 months: pain (5) (...)	26
Peterson 1998	Periosteum	92 (...)	Graft failure (7) (due to graft delamination or central wear of the graft) No serious complications reported, when followed for 8 years adverse events were <10% (no further data provided)	7
Peterson et al 2003	Periosteum	58 (...)	Clinical failure (not defined) (2) (at 14 and 16 months postoperatively) Graft failure (1)	3
Pietschmann et al 2009	NOVOCART 3D	30 (30)	Implant failure associated with infection (1) (patient received new MACI) Implant failure associated with persistent pain (1) (patient received new MACI) Persisting indeterminate pain and effusion (1) (no explanation for complaints found) Arthrofibrosis in suprapatellar recessus (4) (...) Partial detachment of the scaffold (1) (the free rim was trimmed and microfracture performed on the uncovered defect). Requirement for second-look arthroscopy (6) (not implant failure patients, with reported adverse events mentioned above)	8
Robertson et al 2007	Chondrogide	31 (...)	Deep vein thrombosis (1) (patient was anti-coagulated) Superficial wound infections (2) (successful treatment with antibiotics) Focal area of graft hypertrophy that became symptomatic (1)(successfully treated with	5

			arthroscopic debridement) Partial graft failure (1) (...)	
Rogers et al 2009	Porcine collagen membrane	57 (...)	Graft hypertrophy (3) Manipulation of the knee under anaesthesia (3) Graft failures (0)	6
Rosenberger et al 2008	Periosteum	56 (...)	Second-look arthroscopy for periosteal hypertrophy (19) Second-look arthroscopy for arthrofibrosis (3) Second-look arthroscopy for other symptoms (2) The second-look arthroscopy provided lasting relief in 88% of these patients Treatment failure (8) (3 underwent total knee replacement, 2 underwent patellofemoral replacement, 1 underwent a unicompartmental knee replacement, 1 underwent a revision ACI procedure, 1 underwent an osteochondral allograft to the medial femoral condyle) Reasons for failure: Arthrofibrosis (3) Inadequate pain relief (3) Delamination (2)	32
Steinwachs et al 2007 ^a	Type I/III collagen membrane	63 (...)	Incomplete defect filling (3) (all had revision ACI and could perform their activities of daily living, including sports) Graft hypertrophy (2) (asymptomatic) (no revision surgery required)	5
Wondrasch et al 2009 ^a	HyalograftC and CaRes collagen type I gel	31 (31)	Infection (0) Thrombosis (0) Arthrofibrosis (0) Graft delamination (0)	0
Wood et al 2006	Periosteum	294 (...)	Graft failure (73) Delamination (65) Tissue hypertrophy (52) Chondromalacia (37) Adhesions (37) Loose bodies (28) Meniscal tear (26) Local infection (21) Patellar maltracking (21) Arthrofibrosis (16) Plica formation (14) Pain (4) Haematoma/haemarthrosis (4) Other mechanical complications (68) Other (17) Other systemic complications (14) Reoperations (389 reoperations among 273 patients) (93% of all patients with reported adverse events) <i>Cartilage procedures (187):</i> Debridement shaving (85)	497

			Chondroplasty (78) Microfracture (12) Abrasion arthroplasty (4) Drilling (3) Osteochondral autograft (3) Mosaicplasty (1) Osteoarticular allograft (1) <i>Periarticular soft-tissue procedures (97):</i> Lysis of adhesions (25) Lateral release (20) Synovectomy (15) Manipulation (12) Plica resection (12) Scar tissue removal (10) Neuroma excision (3) <i>Corrective intra-articular procedures (63):</i> Removal of loose bodies (26) Meniscectomy (18) Palletoplasty (8) Meniscus repair (6) Anterior cruciate ligament repair (4) Posterior cruciate ligament repair (1) <i>Resurfacing/realignment procedures (29):</i> Corrective osteotomy (15) Total knee replacement (8) Patellar realignment (6) Aspiration/irrigation/drainage/lavage (13)	
Yates 2003	...	24 (24)	Failure within 6 months due to graft delamination (2) Continuous symptoms and failure at two years (1) Serious or deep infections (0) Severe quad atrophy that delayed rehabilitation (8) Flexibility restrictions that required manipulation (4) Reoperation for lysis of adhesions (3) Traumatic falls following implantation (3)	21
TOTAL ADVERSE EVENTS				1025

ACI: autologous chondrocyte implantation; ACI-C: autologous chondrocyte implantation-collagen; AMZ: anteromedialization; DVT: deep vein thrombosis; ICRS: International Cartilage Repair Society; ... = not reported

^acomparative studies treated as case series

^bGobbi et al 2006 and Gobbi et al 2009 report on the same patient population. Gobbi et al 2009 reports on an additional two patients than Gobbi et al 2006 while Gobbi et al 2006 reports an additional adverse event (fibrosis in 1 patient) not reported by Gobbi et al 2006. Study characteristics are for Gobbi et al 2009

^cone patient awaiting one year arthroscopy excluded

^dthe data presented covers only 24 evaluated patients

^eOnly grade 2 and above hypertrophy resulted in patients experiencing symptoms. Grade 1 did not experience symptoms, therefore not included

^fGraft failure defined a priori to be a reoperation when it necessitated removal of the graft or where there was a confirmed loss of defect fill

Appendix G Case series safety data: cartilage defects of the ankle

MACI/ACI for treating cartilage defects of the ankle was reported in six case series, and the characteristics of these studies are presented in Table 23. Three studies used the ACI technique where chondrocytes were injected into the prepared site (Baums et al 2006; Giannini et al 2009; Koulalis et al 2004), and three used the MACI technique (Giannini et al 2005; Giannini et al 2008; Schneider and Karaikudi 2009). The sample size in the studies was generally small, although the length of follow-up was at least one year in all studies.

Table 23 Characteristics of studies providing level IV safety evidence on chondral defects of the ankle

Study ID Study period	Patient allocation	No. of patients (ankles)	Age (years) (mean ± SD)	Male / Female	Length of follow-up (months)	Lost to follow-up
ACI						
Baums et al 2006 ...	Prospective, consecutive	12 (12)	29.7 (range: 18–42)	5/7	Mean: 63 (range: 48– 84)	...
Giannini et al 2009 1997–1999	...	10 (10)	25.8 ± 6.4 (range: 16–49)	5/5	Mean: 119 ± 6.5	...
Koulalis et al 2004 1997–2000	...	10 (10)
MACI						
Giannini et al 2005	20 (only 16 patients operated on) (16)	30.5 ± 8	11/9	range: 12– 20	...
Giannini et al 2008 2001–2004	Consecutive	46 (46)	31.4 (range: 20–47)	29/17	Mean: 36	0
Schneider and Karaikudi 2009 2003–2006	Consecutive	20 (20)	36.2 (range: 19–61)	7/13	21.1 (range: 9–42)	...

ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation; SD: standard deviation; ...: not reported

Adverse events reported in the case series are presented in Table 24. Four of the six studies (84 patients) reported that no complications were observed following MACI/ACI. One study reported that postoperative restriction of ankle flexion due to adhesions occurred in three out of 10 patients, while another study reported a range of adverse events, with seven out of 20 patients requiring additional surgery. Overall, the patient population presented in the case series is too small to make definitive conclusions regarding the rate of adverse events following MACI/ACI in the ankle.

Table 24 Adverse events reported in studies providing level IV evidence on chondral defects of the ankle

Study	Flap/matrix type	No. of patients (ankles)	Adverse events (number of events) (resolution of adverse event, where reported)	Total adverse events
ACI				
Baums et al 2006	Periosteum	12 (12)	Serious complications (deep vein thrombosis, joint infection, or non-union of the osteotomy site) (0)	0
Giannini et al 2009	Periosteum	10 (10)	'No intraoperative or postoperative complications were reported' (0)	0
Koulalis et al 2004	Periosteum	10 (10)	Postoperative restriction of dorsal ankle flexion due to intracapsular adhesions (3) (required arthroscopic adhesiolysis and physiotherapy to restore ankle motion)	3
<i>ACI subtotal</i>		32		3
MACI				
Giannini et al 2005	Hyalograft-C	16 (16)	'Neither subjective nor objective complications were observed with the surgical procedure' (0)	0
Giannini et al 2008	Hyalograft-C	46 (46)	'No intraoperative or postoperative complications were reported' (0)	0
Schneider and Karaikudi 2009	Porcine collagen	20 (20)	Anterior graft impingement (2) Recurrent pain associated with hardware (2) Failures with persistent pain and synovitis (2) (graft removed in 1 patient) Additional surgery required (7 patients required a combination of procedures including 5 cases of hardware removal, 3 cases of arthroscopic ankle debridement, 1 case of posteromedial release of ankle with tendoachilles lengthening)	ND ^a
<i>MACI subtotal</i>		82		ND
Total		114		3

ACI: autologous chondrocyte implantation; MACI: matrix-induced autologous chondrocyte implantation; ND: not determined; ... = not reported

^aTotal number of adverse events could not be determined from this study, due to unclear overlap in patients and procedures

Appendix H Results of assessment: critical appraisal

Table 25 Critical appraisal of non-randomised comparative studies

Study	Study design	Sample size	Outcomes			Statistical methods	Duration of follow-up
			Safety	Effect.	Description		Losses to follow-up
Level III-2							
Derrett et al 2005 ^a	Cross-sectional retrospective cohort study (concurrent controls). A third group of ACI waiting list patients was used to provide information about the knee-related and general health status of preoperative patients (n=22). Blinding not reported.	Total: 73 patients ACI: 53 patients (patients included in the Bentley et al 2003 study received ACI-P and ACI-C) Mosaicplasty: 20 patients	•	•	Modified Cincinnati Knee Rating System Pain Disability Index (PDI) EQ-5D Resources used (e.g. surgery costs, inpatient cost – main surgical episode, inpatient days – other, day case days, outpatient visits, MRI scans, histology, x-rays). Unanticipated outpatient appointments, day case and inpatient admissions, and reoperations.	Statistical tests described: Statistical Package for Social Sciences (SPSS). The percentile method was used to generate 95% confidence intervals. Significance level stated: only results with $P \leq 0.05$ were interpreted as having statistical significance.	Clinical progress was reviewed at 6 weeks, 12 weeks, 6 months, 9 months, 12 months, and then twice yearly. After 1 year, all patients underwent arthroscopic assessment of the graft and biopsy when possible. Secondary-care resource use was collected to 2 years postoperatively. Given the cross-sectional retrospective design of the study, participants were unable to complete the postal questionnaire at a consistent time postoperatively. Losses to follow-up: only 44 ACI patients, 12 mosaicplasty patients and 20 waiting list patients completed the postal questionnaire
Fu et al 2005	Retrospective observational cohort study (concurrent controls) (analyses performed retrospectively on prospectively collected follow-up data).	Total: 116 patients ACI-P: 58 patients Debridement: 58 patients Debridement: the mechanical removal of loose cartilage fragments or flaps back to a stable rim of normal-	•	•	Modified Cincinnati Knee Rating System.	Statistical tests described: SPSS statistical package (version 12.0, SPSS Inc., Chicago, ILL); 2-sample Student t-tests; Pearson χ^2 test; Fisher exact test; Kolmogorov-Smirnov test; Wilcoxon signed rank test; Mann-Whitney U test; logistic	Follow-up: at least 3 years. Losses to follow-up: outcome assessments were completed by 54 ACI patients and 42 debridement patients

		appearing cartilage. This procedure was distinct from marrow stimulation procedures (MST) because it did not involve the perforation of the subchondral bone to stimulate bleeding.				regression model. Significance level stated: all <i>P</i> values were 2-tailed and considered significant at the 0.05 level.	
Kon et al 2008	Prospective non-randomised cohort study (concurrent controls).	<p>Total: 80 patients ACI (unclear whether ACI-P or ACI-C) : 40 patients Microfracture : 40 patients</p> <p>Microfracture: after identifying the full-thickness chondral lesion, we removed the unstable cartilage, including cartilage loosely attached to the surrounding rim, using a shaver and/or a handheld angled curette. When present, the calcified layer of cartilage was also removed using a curette. Once the exposed subchondral bone plate was thoroughly debrided, we made multiple holes using a Steadman arthroscopic pin. The holes were placed perpendicular to the joint surface, approximately 3 to 4 mm apart and about 2 to 4 mm deep, with care taken not to damage the subchondral plate between the holes. Once the holes were completed, the irrigation fluid pump pressure was lowered to visualise the release of fat droplets and blood from the microfracture holes into the knee.</p>	•	•	IKDC: International Knee Documentation Committee Tegner score Cartilage standard evaluation form as proposed by the International Cartilage Repair Society	<p>Statistical tests described: Kolmogorov-Smirnov test; nonparametric test; Wilcoxon test; Mann-Whitney test; Kruskal-Wallis test; Pearson's χ^2 test; Spearman rank correlation analysis; r-b Kendall correlation analysis; Statistical Package for the Social Sciences (SPSS). Significance level stated: for all tests, $P < 0.05$ was considered significant.</p>	<p>Follow-up: preoperative, 2- and 5-year follow-up Losses to follow-up: 0 (authors stated that all 80 patients were evaluated preoperatively at 2 and 5 year follow-up).</p>

Salzmann et al 2009	Non-randomised comparative cohort study. Probably retrospective – patients were matched for postoperative interval.	Total: 18 patients MACI: 9 Osteochondral autograft transplantation (OAT): 9 patients OAT: the cartilage defects in all patients treated by OAT were assessed arthroscopically and subsequently by an open approach. The diameter of the transplanted cylinders was 10 mm in every patient with a mean number of 1.5±1.0 transplanted cylinders	•	•	Modified Lysholm score Modified Cincinnati knee rating system Visual Analog Scale (VAS) for pain Tegner activity scale Short Form-36 (SF-36) MRI analyses: T2 index; MOCART score	Statistical tests described: SPSS; covariance analysis; Wilcoxon test; Spearman's correlation coefficient. Significance level stated: $P < 0.05$ was considered to indicate statistical significance	Follow-up: MACI: mean 42.0±17.4 months, range 25-77 months OAT: mean 41.3±16.5 months, range 23-75 months Losses to follow-up: 0 (calculated from data provided in tables)
Trattng et al 2008	Non-randomised comparative cohort study. Probably retrospective – patients were matched for postoperative interval.	Total: 20 patients MACI (Hyalograft®C, a hyaluronan based matrix): 10 patients Microfracture: 10 patients Microfracture: during arthroscopy, loose cartilage bodies were removed and marginally attached cartilage was debrided. After exact preparation of the bed, an arthroscopic 70°-angled awl was used to penetrate the subchondral plate and to generate micro-holes in the exposed bone starting in the periphery of the lesion. Subchondral plate integrity was ensured by maintaining a minimum distance of 3 mm between the micro-holes.		•	Lysholm score MRI examination (T1 GRE technique; gold-standard T1 IR technique)	Statistical tests described: ANOVA; Pearson coefficient; SPSS version 15.0. Significance level stated: $P < 0.05$ was considered statistically significant	Follow-up: MACI: mean 32.0±17.2 months Microfracture: mean 33.0±17.3 months Losses to follow-up: 0 (calculated from data provided in text)
Welsch et al 2008a ^b	Non-randomised comparative cohort study. Probably retrospective –	Total: 20 patients MACI (Hyalograft C, a hyaluronan-based scaffold):	•	•	Lysholm score MRI examination (T2 values)	Statistical tests described: three-way analyses of variance with random effects and two	Follow-up: Authors subdivided each patient group into a shorter and a

	patients were matched for postoperative interval.	10 patients Microfracture: 10 patients				repeated-measure factor; SPSS version 14.0. Significance level stated: $P < 0.05$ was considered statistically significant	longer imaging follow-up group, with 5 patients per group (group 1: 12-24 months; group 2: >24 months). Group 1: MACI: mean 17.6 months (range 12-22) Microfracture: mean 18.0 months (range 12-24) Group 2: MACI: mean 37.2 months (range 26-54) Microfracture: mean 38.8 months (range 28-64) Losses to follow-up: nil (calculated from data provided)
Welsch et al 2008b ^b	Prospective, non-randomised, comparative cohort study.	Total: 34 patients MACI (HyalograftC, a hyaluronan-based scaffold): 17 patients Microfracture: 17 patients Microfracture: an arthroscopic, one-step surgical procedure using a specially designed awl to perforate the subchondral bone plate multiple times. The released blood from the bone marrow, including mesenchymal stem cells and growth factor, forms a clot that, over time, transforms into cartilage repair tissue that has been reported as fibrocartilaginous tissue in several studies.		•	MRI analyses: MTR mapping; T2 mapping	Statistical tests described: Three-way ANOVA with random effects and two repeated measure factors; Pearson correlation; SPSS version 15.0. Significance level stated: $P < 0.05$ was considered statistically significant	Follow-up: at 36.6±19.6 months. Microfracture: MRI performed at 30.2±18.2 months postoperatively (range 11-64 months). Patients were divided into 2 groups: shorter (11-29 months) follow-up (12 patients) and longer (42-64 months) follow-up (6 patients). MACI: MRI performed postoperatively (range 12-68 months). Patients were divided into 2 groups: shorter (12-31 months) follow-up (10 patients) and longer (51-68 months) follow-up (7 patients). Losses to follow-up: ...
Welsch et al 2009 ^b	Non-randomised comparative cohort study. Probably retrospective –	Total: 20 patients MACI (Hyalograft©C, a hyaluronan-based scaffold): 10 patients		•	Clinical evaluation: Lysholm score Morphological evaluation: MOCART	Statistical tests described: three-way analysis of variance (ANOVA) with random effects with two repeated measures; Pearson coefficient; SPSS	Follow-up: MACI: 31.7±18.3 months postoperatively (range 12-59) Microfracture: 32.6±16.7

	patients were matched for postoperative interval.	Microfracture: 10 patients			Biochemical evaluation: T2; DWI	version 15.0. Significance level stated: $P < 0.05$ was considered statistically significant	months postoperatively (range 12-63) Losses to follow-up: 0 (calculated from tables provided)
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ACI: autologous chondrocyte implantation; ACI-C: autologous chondrocyte implantation-collagen; ACI-P: autologous chondrocyte implantation-periosteum; ANOVA: analysis of variance; DWI: diffusion-weighted imaging; EQ-5D: EuroQuol Group 5-Dimension Self Report Questionnaire; IKDC: International Knee Documentation Committee; MACI: matrix-induced autologous chondrocyte implantation; MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue; MR: magnetic resonance; MRI: magnetic resonance imaging; MST: marrow stimulation technique; MTR: magnetic transfer ratio; OATS: osteochondral autograft transplantation; PDI: Pain Disability Index; SF-36: Short Form-36; SPSS: Statistical Package for Social Sciences; VAS: Visual Analog Scale

^aThis study includes a subset of patients (intervention and comparator group) from Bentley et al, 2003. 'A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee', *Journal of Bone and Joint Surgery (British)*, 85-B, 223-230

^bThere is potential patient overlap between Welsch et al 2008a, Welsch et al 2008b and Welsch et al 2009

Appendix I Scoring systems

Table 26 Outerbridge and ICRS classification systems for cartilage defects

Outerbridge grade	ICRS grade	Description
	0	No defects
I	1a	Surface intact, fibrillation, and/or softening or swelling
	1b	Additional surface lesions
II	2	Fragmentation or fissuring in area \leq 0.5 inches in diameter. Lesion depth up to 50% of cartilage thickness
III	3a	Fragmentation or fissuring in area $>$ 0.5 inches in diameter. Lesion depth greater than 50% but not to calcified layer
	3b	Lesion depth greater than 50% to calcified layer
	3c	Lesion depth greater than 50% to subchondral plate.
IV		Cartilage erosion to bone level (exposed subchondral bone)

Source: Outerbridge RE, 1961. 'The aetiology of chondromalacia patellae', *Journal of Bone and Joint Surgery (American)*, 43, 752-757
 ICRS: International Cartilage Repair Society

Table 27 Knee function classification and scoring systems

Scoring system	Best/worst score	Description
Lysholm	Best: 100/Worst: 0	The scores require patient collaboration. Items include limp, requirement for support, stair-climbing, squatting, walking, running and jumping, pain, swelling, and thigh atrophy (Lysholm and Gillquist 1982). Evaluation is usually completed with use of the Tegner activity score (maximum 10 points) (Briggs et al 2009).
Tegner	Best: 10/Worst: 0	This is a knee-specific scoring system which discerns a person's activity level between 0 and 10, where 0 is sick leave or disability pension because of knee problems and 10 is participation in competitive sports such as soccer at a national and international elite level (Tegner and Lysholm 1985).
Noyes (Cincinnati)	Best: 10/Worst: 0	The components of knee function include walking, stairs, squatting or kneeling, straight running, jumping or landing, and hard twists or cuts or pivots. Rated symptoms include pain, partial giving-way and full giving-way. Other scales may be incorporated to produce a final rating, including a sports rating scale (100-0 points), functional scale assessing daily living activity (120-0 points), sporting activity (100-0 points) and aspects of clinical examination (Noyes et al 1989).
Knee Society	Best: 200/Worst: 0	This two component scoring system evaluates outcome of knee arthroplasty and assesses pain, function (walking and stair climbing) and clinical features (range of motion, stability, alignment, flexion contracture and extension lag). The first component assesses pain (50 points), stability (25 points) and range of motion (25 points). The second component assesses walking distance (50 points) and stair-climbing (50 points) (Insall et al 1989).
Hospital for Special Surgery	Best: 100/Worst: 0	This scoring system is based on symptom severity and clinical examination. The system includes function (walking, transferring and climbing stairs; 22 points), pain (30 points), range of motion (18 points), muscle strength (10 points), deformity (10 points) and instability (10 points) (Ranawat, Insall and Shine 1976).
International Knee Documentation Committee (IKDC)	Best: 100/Worst: 0	This system assesses function, symptoms, range of motion and ligament of examination. The following scale is used for ratings: normal, nearly normal, abnormal and severely abnormal (Irrgang et al 1998).
Knee injury and Osteoarthritis Outcome Score (KOOS)	Best: 100 (per category)/Worst: 0 (per category)	This system assesses the categories of symptoms, pain, activities of daily life, sports and recreation, and knee-related quality of life. The score is often reported as a mean of all subclasses with individual category scores reported when they differ from the average result (Kunzl et al 2009).
Short Form 36 (SF-36)	Best: 100 (per scale)/Worst: 0 (per scale)	This system consists of eight scaled scores, measuring the total state of the patient. The survey assesses vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social functioning, and mental health (Bartlett et al 2005).
Visual Analog Score (VAS)	Best: 0/Worst: 10	This score consists of a 10 cm line with 0 on one end (no pain) and 10 on the other (worst pain experienced by the patient) (Kelly AM 2001).
Kellgren and Lawrence Radiographic Grading of Osteoarthritis	Best: 1/Worst: 4	This system comprises four radiographic scores. These include 1 (minute osteophyte, doubtful importance), 2 (definite osteophyte, undiminished joint space), 3 (moderate diminution of joint space) and 4 (joint space greatly diminished with sclerosis of subchondral bone) (Knutson et al 2007).
EuroQol Group 5-Dimension Self Report Questionnaire (EQ-5D)	Best: 11111 (per health state)/Worst: 33333 (per health state)	This descriptive system consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), where each dimension has three levels of severity (no health problems, moderate health problems, extreme health problems). A total of 243 health states are included and have an associated 5-digit descriptor, where 11111 represents perfect health and 33333 represents the worst possible state (Agency for Healthcare Research and Quality 2005).
Meyers	Best: 18/Worst: <12	This rating scale assesses pain (range 1-6 points), function (range 1-6 points) and range of motion (range 1-6 points). A total score of 18= excellent, 15 to 17 points= good, 12 to 15 points= fair and less than 12 points= poor (Meyers et al 1989).

Appendix J Excluded studies

No safety data

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