

Autologous chondrocyte transplantation for cartilage defects in the knee joint

A West Midlands Development and Evaluation Service Report

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**West Midlands Development and Evaluation Committee
Recommendation:**

The recommendation for Autologus Chondrocyte Transplantation was:

Not Supported – for routine use

The procedure should only be performed as part of a randomised controlled trial.

Anticipated expiry date: 2003

- This report was completed in November 2000
- The searches were completed in December 1999
- Randomised trials comparing ACT with other interventions are at present recruiting patients. It is possible, but unlikely, that recruitment will be completed within 2 years in most cases. Follow-up data for a minimum of 2 years is essential in all cases. Therefore this report is likely to be valid until 2003, at least, unless compelling data becomes available from observations in established cohorts of patients.

Question addressed by this review:

Is chondrocyte transplantation effective in the treatment of hyaline cartilage loss in knee joints?

Conclusions

Knee injuries arising from sporting activity are common. Such injuries can lead to knee hyaline cartilage damage (as opposed to meniscal injuries which are also referred to as 'cartilage' damage by lay-persons). How commonly hyaline cartilage damage occurs is not clear, and the natural history of such injuries is poorly understood. Orthopaedic and trauma surgeons use a variety of techniques to treat these lesions but few treatments, including autologous chondrocyte transplantation, have been tested in controlled studies. This report is based on studies of patient cohorts with hyaline cartilage defects. These studies indicate that, over a period of 2 years, 60-70% of patients have improved symptoms with a variety of treatments.

In the absence of controlled trials autologous chondrocyte transplantation should be regarded as an experimental therapy. It is recommended that suitable patients are included in randomised trials co-ordinated at a National level. Routine commissioning of this procedure cannot be recommended. However since any experimental surgical procedure is subject to a learning curve it is recommended that chondrocyte transplantation is supported, for limited indications, and performed by a limited number of surgeons, in order that a therapeutic option is available for difficult clinical problems.

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About West Midlands Development and Evaluation Service

The West Midlands Development and Evaluation Service (DES) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

About InterTASC

West Midlands DES is a member of InterTASC which is a national collaboration with three other units who do rapid reviews: the Trent Working Group on Acute Purchasing; the Wessex Institute for Health Research and Development; York Centre for Reviews and Dissemination.

The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing and quality control of reports.

Contribution of Authors

Paresh Jobanputra conducted searches, made contacts with industry representatives and with leading researchers in the field, applied inclusion and exclusion criteria, extracted and organised the data, conducted the economic analysis with David Parry, and wrote this report. David Parry assisted in making contacts with leading researchers, provided early background material and data from preliminary searches, assisted with the economic analyses, and helped edit the report. Catherine Meads independently extracted data from studies of chondrocyte transplantation and was involved in helpful discussions. Amanda Burls initiated this project, provided constant support and encouragement during the conduct of the research and edited the report.

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Conflict of Interest

This work has been undertaken by staff funded by the NHS. Paresh Jobanputra has received no funding from any sponsor in this work and was granted study leave from University Hospital Birmingham NHS Trust.

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In the absence of controlled trials autologous chondrocyte transplantation should be regarded as an experimental therapy. It is recommended that suitable patients are included in randomised trials co-ordinated at National level. Routine commissioning of this procedure cannot be recommended.

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DP assisted in making contacts with leading researchers, provided early background material and data from preliminary searches, assisted with the economic analyses, and helped edit the report.

CM independently extracted data from studies of chondrocyte transplantation and was involved in helpful discussions.

AB initiated this project, provided constant support and encouragement during the conduct of the research and edited the report.

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Summary

Description of procedure

Autologous chondrocyte transplantation (ACT) is a novel surgical approach used for the treatment of full thickness cartilage defects in knee joints. Small grafts of normal cartilage removed from a diseased joint are treated in a laboratory to obtain cartilage cells. These are cultured to expand the cell population and subsequently re-implanted, a few weeks later, into areas where cartilage is denuded. The aim of this procedure is to restore normal cartilage to the ends of bones and thereby restore normal joint function. This treatment is not funded by Health Authorities and is not routinely available although a few procedures have been carried out by a small number of surgeons.

Epidemiology

There are no reliable estimates of the prevalence of cartilage defects in the knee. Lesions are most likely to arise in sportsmen and women as a result of injury. Up to 20% of those sustaining a haemarthrosis following a knee injury may have cartilage damage.

Number of studies and quality of evidence

Thirty-seven reports on ACT were identified. Of these 24 were excluded, 15 because they were reviews or news features, the remainder because they lacked relevant data or because of data duplication. All included reports were case series with a variable length of follow-up. With one exception all studies reported improvement in patient status usually over a follow-up period of less than 2 years.

Summary of outcomes

Overall outcome of ACT surgery was rated 'good' or 'excellent' by approximately 70% of patients over a 2-year period, in the largest patient series reported. On average 15% of patients required further arthroscopic surgical procedures during follow-up. Between 3 and 7% of patients were judged to have failed treatment. For comparator treatments between 10% and 95% of cases were rated 'good' or 'excellent' over a 2-year period. Since ACT can result in repair of cartilage defects with true hyaline cartilage, it may provide a more durable clinical response with longer follow-up.

Costs and Cost per QALY

Over 10 years the expected cost of treating patients with ACT was estimated at £10,400 compared with £3,000 for other options for treating cartilage defects, a difference of £7400. An estimate of the expected cost per QALY gained with ACT was £9000 (best case £1700, worst case £13,700).

Limitations

The reported literature is subject to bias because of the inherent weaknesses of case series. In addition the long-term impact of conventional surgical treatments, or no surgical treatment, is poorly documented. In determining costs and cost-utility a large number of assumptions were required which should caution against over reliance on these figures.

List of abbreviations

ACT Autologous Chondrocyte Transplantation
ACL Anterior Cruciate Ligament
BHA Birmingham Health Authority
DEC Development Evaluation Committee
QALY Quality Adjusted Life Year
OA Osteoarthritis
OCD Osteochondritis Dissecans
MRI Magnetic Resonance Imaging
TKR Total Knee Replacement

Definition of terms

Arthroscopy

Examination of the internal structure of a joint, by means of a fibre-optic scope.

Avascular necrosis

Damage to bone and cartilage due to a local loss of blood supply.

Cartilage defect or chondral defect (or fracture)

Loss of cartilage lining the end of a bone; of variable thickness.

Cost-minimisation

Economic analysis used when outcomes are the same irrespective of intervention used. The aim is to determine the most efficient way of achieving a given goal.

Cost-utility analysis

A form of economic evaluation that uses a generic measure of health, for example a quality adjusted life year, as a way of expressing the outcome of a particular treatment. It seeks to answer the question 'what is the most efficient way of spending a given budget'.

Osteochondral defect

Loss of cartilage and bone at a joint

Osteochondral fracture

Loss of cartilage and bone at a joint as a result of injury

Osteochondritis dissecans

Detached fragment of cartilage with or without bone, at a joint, arising spontaneously or as a result of injury.

Osteoarthritis

A disease of joints in which there is evidence of cartilage loss and an accompanying reaction in bone.

Hyaline cartilage

Cartilage that is usually found at the ends of bones, within a synovial joint.

1 Aim of review

The aim of this review was to evaluate the risks, benefits and economic costs of chondrocyte transplantation for the treatment of hyaline cartilage loss in knee joints. Specific objectives were first, to identify types of knee disease for which chondrocyte transplantation has been applied. Second, to describe the natural history of these conditions. Third to describe alternative treatment options. Fourth, to determine long term outcomes, and finally to analyse the economic efficiency, specifically cost-utility, or gains from this procedure expressed as quality-adjusted life years (QALY).

Population: Patients who have symptomatic cartilage defects that have arisen either as a result of injury or an unknown cause but not as a result of a well established arthritic disorder such as rheumatoid arthritis or osteoarthritis.

Intervention: Autologous chondrocyte transplantation in knee joints. Defined as implantation of autologous chondrocytes that have been cultured in a laboratory, in order to expand the cell population, and subsequently returned to the diseased knee joint from which they were obtained.

Outcomes: Any clinical outcomes including patient and clinician opinion, symptom assessment scores, knee scoring indices and general health status assessments; with the exclusion of histological scores.

Statement of question: How effective, and cost-effective, is autologous chondrocyte transplantation, compared with other surgical treatment options, for patients with knee hyaline cartilage defects?

2 Background

2.1 Origin of request and scope of report

This DEC report was requested by Dr Steve Munday, of Birmingham Health Authority (BHA). It follows a request for funding to BHA by the Royal Orthopaedic Hospital, in Birmingham, to carry out a limited number of these procedures. This is a novel and expensive procedure and it was felt that the indications, alternative treatment options, and outcomes of chondrocyte transplantation should be reviewed in detail.

This report focuses on clinical studies in humans in which living hyaline cartilage has been removed from a diseased knee joint, at arthroscopy, and treated in a laboratory to isolate cartilage cells (chondrocytes). Isolated chondrocytes are cultured to expand cell numbers and re-implanted into the diseased knee at a second, open, surgical procedure requiring arthrotomy. The purpose of this procedure is to heal breaches or defects of normal hyaline cartilage in diseased joints. This report is concerned with the use of chondrocyte transplantation in any disease of the knee joint in which it has been applied. Cartilage, in this review, refers to hyaline cartilage, which is found lining the ends of bones, at a joint, and also includes cartilage lining the kneecap (patella). This report is not concerned with diseases of menisci (colloquially, also referred to as 'cartilage', see Figure 1, page 21) except where this is directly relevant to chondrocyte transplantation.

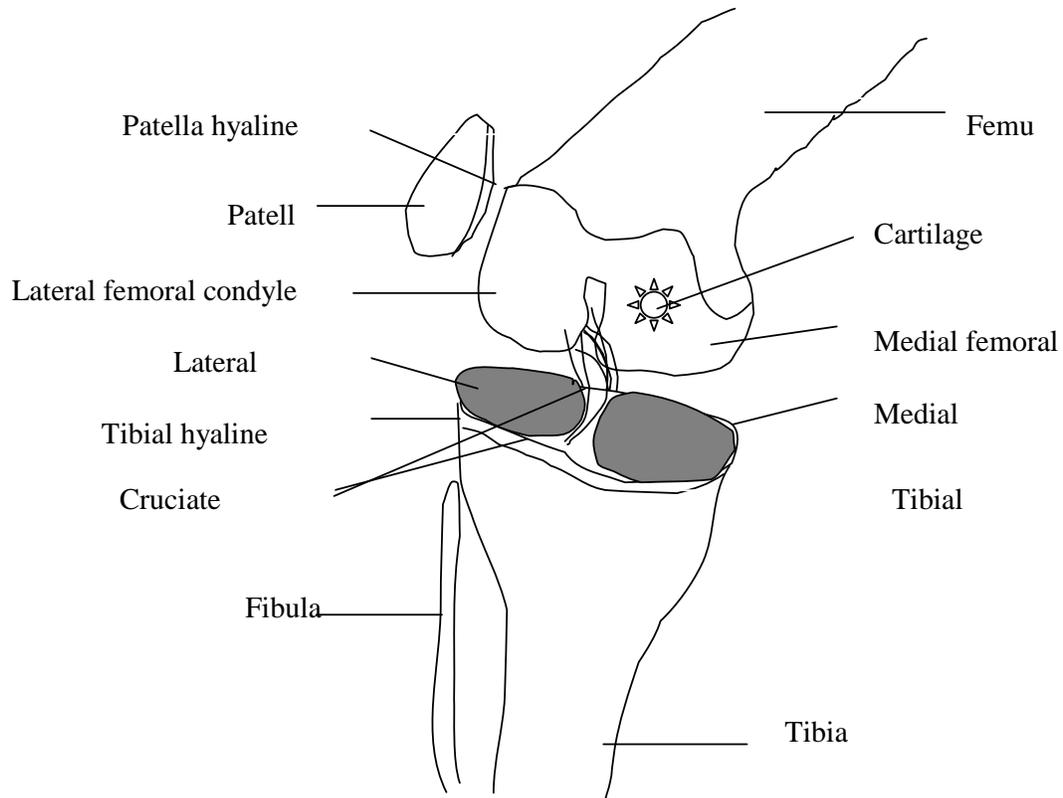
2.2 Nature of the problem

Hyaline cartilage, if it is damaged, has only a limited capacity for repair. Normal hyaline cartilage provides a smooth surface at the ends of bones that allows virtually frictionless movement within a joint. This tissue is composed of a meshwork of type II collagen within which proteoglycans, a complex protein-carbohydrate biochemical, is entrapped (reviewed in reference 1). Proteoglycans are hydrophilic and cartilage retains a considerable amount of water under tension within the collagen meshwork. Damage to joint cartilage results in breaks in this collagen meshwork and other changes in the chemical composition of cartilage. The normal function of a joint is impaired with loss of the normal smooth surface of joint cartilage. Since cartilage has a limited capacity for repair significant damage can lead to premature joint failure and a requirement for joint replacement surgery.

Cartilage damage may be classified in a variety of ways. One widely used scheme classifies cartilage damage into 5 grades (grade 0 is normal cartilage, to grade 4). In grade 1 there is softening and swelling of cartilage without significant surface damage whilst in grade 4 there is erosion and complete loss of cartilage down to bone². An injury to a joint can cause hyaline cartilage damage and damage to bone. This is known as an osteochondral fracture. Loss of cartilage alone is referred to as a chondral fracture. Osteochondral fractures occur more commonly in adolescents. It appears that the plane of weakness at a joint, in adolescents, lies in bone rather than at the junction of cartilage and bone^{3,4}. Cartilage damage can be caused directly from injury, or in various types of arthritis, or it may be secondary to other disorders which cause knee instability, such as ligament insufficiency or diseased menisci. The term osteochondritis dissecans (OCD) usually refers to a condition in which there is spontaneous loss of a fragment of bone and cartilage from a joint. In young persons the most common causes of hyaline cartilage damage are sporting injuries.

The natural history of hyaline cartilage defects that follow injury is not known. Cartilage lacks a nerve supply and isolated cartilage damage does not directly cause pain. Thus a proportion of patients with significant cartilage defects do not experience pain and may not experience any other symptoms associated with knee injury. Unrecognised injury during sporting or other physical activity may lead to an increased risk of developing osteoarthritis. Symptoms associated with loss of cartilage, of full thickness, are similar to those of a meniscal tear⁵, commonly referred to as a 'torn cartilage' (see Figure 1, page 21). Patients complain of knee pain, knee swelling, joint locking (i.e. a joint becomes stuck in one position) and giving way of the joint. Knee injuries of various sorts may cause a chondral or osteochondral defect. For example, a direct shearing force on the medial or lateral femoral condyle due to a heavy fall on a bent knee, or a direct kick on a bent knee, or as a result of patellar dislocation. Rotary forces on the knee whilst weight bearing, for example a sudden or unintended change in direction

Figure 1 - Anatomy of a knee joint



in a skier or footballer may also result in chondral or osteochondral lesions^{3,6}. Cartilage defects are usually diagnosed by arthroscopy⁷, although they may be seen on MRI. Osteochondral fractures, which involve loss of bone and cartilage, may however be seen on X-rays. Osteochondritis dissecans (OCD) resembles osteochondral fractures in that a segment of cartilage and some bone becomes detached from the joint surface. In some studies the two terms osteochondral fractures and OCD are used inter-changeably, causing some confusion. Characteristically OCD is a concentric lesion which involves the medial femoral condyle in a knee and which develops spontaneously, without a precipitating injury. OCD often occurs during the second decade of life⁸. Some believe it arises as a result of localised avascular necrosis of the subchondral bone causing separation of a fragment of bone and cartilage⁹. Long term studies of OCD provide the only source of information on the likely natural history of cartilage defects in a knee joint. For example, Linden found that 55% of adults, but none of the children, developed severe osteoarthritis (OA), in a study of OCD which followed fifty-eight patients for an average of 33 years¹⁰. Linden suggested that tissue repair was more effective in children and that OA, due to OCD, arose in adults some 10 years earlier in life than primary forms of OA.

Osteoarthritis is a heterogeneous disease in which there is focal or widespread loss of cartilage. The cause of OA is unknown but many factors including mechanical and genetic factors may be involved. For instance, studies in sportsmen and women show that activities which cause high impact and torsional loading on joints results in a greater risk of OA¹¹. This supports the notion that cartilage injury arising in such sports may cause OA. There is no precise definition for OA but a current working definition states that OA is 'a condition of synovial joints characterised by cartilage loss and evidence of an accompanying peri-articular bone response¹²'. The term 'peri-articular bone response' refers to an increased density of bone near a diseased joint seen on X-rays and to the formation of new bone at the edge of a joint known as osteophytes. Early OA may not demonstrate this characteristic bony reaction on X-rays¹³. Therefore discrete loss of cartilage seen at arthroscopy may be attributed to an injury, where there is a clear history of injury, or it may be attributed to early OA where there is no history of injury. It is therefore possible that treatments that are used to treat cartilage defects due to injury, such as ACT, may also be used in early OA which involves a single joint. Other diseases of joints such as rheumatoid arthritis or psoriatic arthritis can also cause cartilage damage. In these diseases cartilage damage occurs because of an inflammatory reaction of soft tissues around the joint, which induces cartilage damage. Also, there are often features of a generalised illness with abnormalities in blood, a feeling of general ill health, and commonly, many joints are involved. It is unlikely therefore that ACT would be used in these conditions.

2.3 Prevalence and incidence

Precise estimates of how often cartilage damage caused by knee injury occurs in a defined population are not available. Also, cartilage damage may arise indirectly from knee injury for example as a result of other sorts of knee injury that cause joint instability or abnormal loading of the knee. Injury to the anterior cruciate ligament¹⁴, or a meniscus¹⁵ can lead to cartilage damage. Patients with knee symptoms are often investigated, and treated, by an arthroscopic examination of the knee joint. Data from a large database of arthroscopies shows that full thickness loss of cartilage, in those under the age of 40, accounts for 5% of all procedures¹⁶. In acute knee injuries where there is a haemarthrosis (bleeding into the joint) around 20% of knees show cartilage surface defects (chondral fractures), often with other damage within the knee such as lesions of the anterior cruciate ligament and of menisci¹⁷. The incidence of OCD, by comparison to injury related cartilage damage, is low and lies

between 6-14 patients per 100,000 population; primarily in those between the ages of 10 and 30 years¹⁸.

Some reports suggest that isolated cartilage damage is relatively uncommon; occurring in only 8 patients from a series of over 1000 arthroscopies¹⁹. However significant cartilage injury, as judged by microscopic appearances of cartilage over areas of 'bone bruising' or bony contusion seen on magnetic resonance images (MRI), appears to be fairly common²⁰. In these cases there is frequently no abnormality of the cartilage surface if the joint is examined by arthroscopy soon after injury. However with time, patients who have sustained a bone bruise seen on an initial MRI, show evidence for cartilage loss in around 50% of cases with follow-up MRI²¹. These data suggest that cartilage damage may frequently go unrecognised. Especially since conventional MRI scans are relatively insensitive for detecting cartilage defects compared with arthroscopy²².

Reports of diagnostic arthroscopy in sportsmen with a haemarthrosis, for example a study from Newham General Hospital in London, found evidence of osteochondral fractures in 15 (14%) of 106 arthroscopies analysed prospectively over 6 years²³. A Swedish orthopaedic department in which all patients with knee injuries had a standardised diagnostic work-up found 940 consecutive cases of knee injury over a 5-year period²⁴. Ninety of these cases with stable knees were examined by arthroscopy and fourteen (1.4% of all knee injuries) were found to have chondral or osteochondral lesions; described by the authors as 'small'. Other reports, for example a study in Washington over 8 months, which describes patients with more serious knee injuries, found 123 (61%) of 200 knees with evidence of cartilage lesions; often associated with other knee injuries²⁵.

2.4 Options for treatment of cartilage defects and rationale for decision pathway

A variety of treatments may be used to treat patients with symptoms from knee cartilage damage. This report is only concerned with surgical treatments. A brief description of common surgical interventions used to treat these is shown in Table 1, page 26. A clinical decision pathway that might be used to treat cartilage defects is shown in Figure 2, page 25. Non-surgical therapy such as physical therapy, the use of braces and supports, measures to reduce weight (and thereby joint loading), the use of analgesics or anti-inflammatory drugs, the use of drugs containing elements of cartilage such as chondroitin sulphate, and many other potential treatments, are not considered in this report.

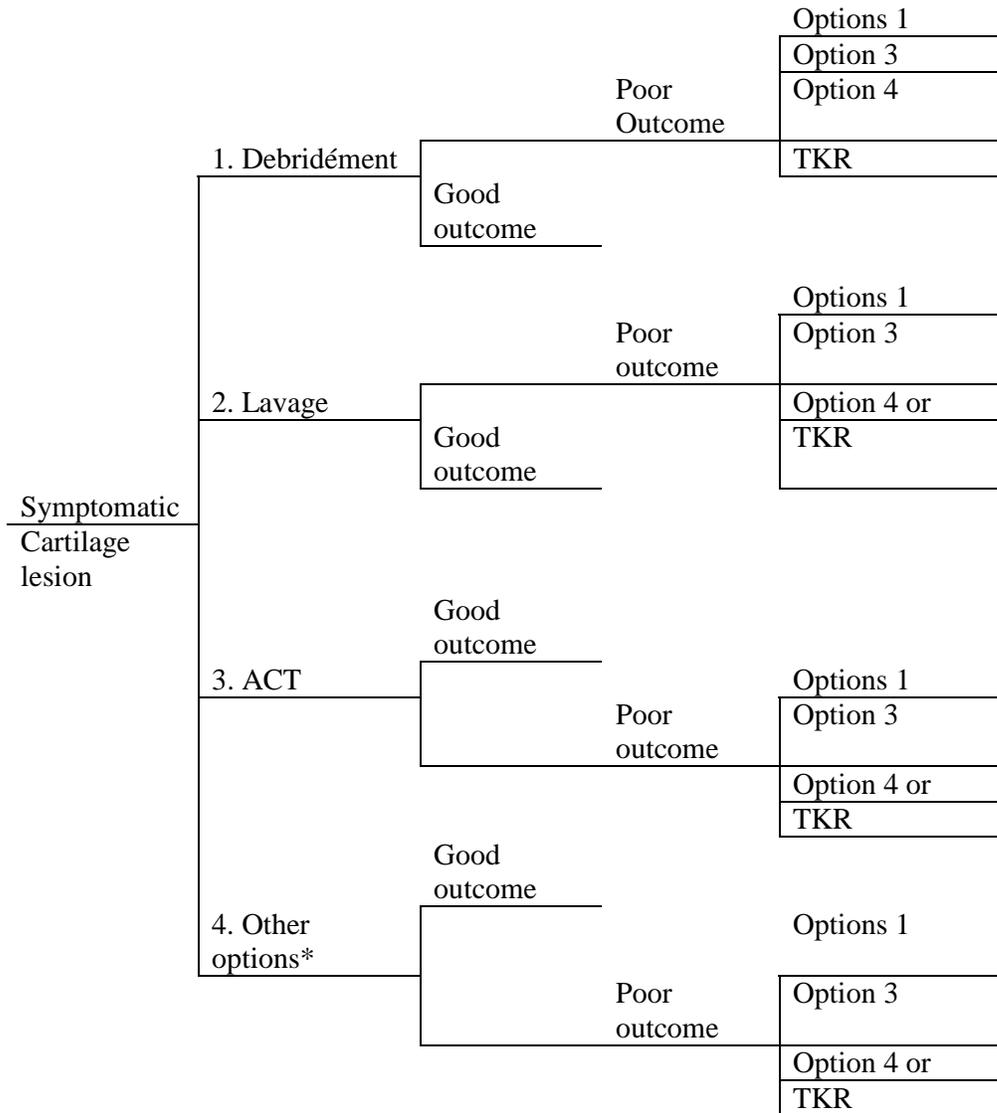
No surgical treatment for cartilage defects has been evaluated systematically, and most reports in the literature describe a series of cases. Many studies describe patients with established OA of the knee with changes on X-rays, rather than patients with localised cartilage loss following knee injury. Proponents of autologous chondrocyte transplantation (ACT) believe that isolated cartilage defects are a precursor of knee OA but regard established OA as a contraindication for ACT. Thus, ACT is contraindicated if both surfaces of a knee joint have full thickness cartilage loss, or there is radiographic evidence of joint space narrowing and bony changes (indicating a more general and severe disease process)²⁶. The available epidemiological evidence shows that joint injury increases the risk of OA particularly if there is a risk of repetitive high levels of impact and torsional loading, and in those with a history of joint injury¹¹.

In constructing the decision tree the absence of a standard surgical approach for cartilage defects created uncertainty as to the optimal pathway for a patient with a symptomatic

cartilage lesion. A choice of pathways based on interviews with 16 US surgeons, carried out by Health Advances Inc. and commissioned by Genzyme, was submitted to the FDA in support of a licence application for commercial use of ACT by Genzyme. A licence was granted in August 1997 but a requirement for randomised studies of ACT was stipulated. The pathway derived for Genzyme²⁷ suggests that all patients with chondral defects would receive a 'fibrocartilage procedure', presumably at least debridement with or without some form of marrow stimulation technique (Table 1, page 26), prior to ACT. This pathway however did not explicitly describe treatment options such as debridement and considered osteotomy and total knee replacement (TKR) at a relatively early stage for example within a time span of 10 years following a 'fibrocartilage procedure'. In the absence of long term follow up data all pathways, based on opinion, can only be speculative. We would regard TKR as a last-resort option in this group of relatively young patients. Studies of OCD suggest that many adults are symptom free for 20 years before they develop evidence of OA¹⁰. In any case neither osteotomy, nor TKR, can be regarded as directly competing therapies for ACT but are later therapeutic options in those with poor outcomes with initial interventions.

We have adopted a simple decision tree which considers a variety of potential options for cartilage defects from the outset and considers the possibility that ACT may be used very early in the treatment of cartilage defects. The most likely pathway for a patient with a cartilage defect is initial treatment by debridement with or without marrow stimulation²⁸. This could be followed by ACT, if symptoms persist, and where this is available. Debridement, marrow stimulation and even ACT may be repeated in an individual if there is failure to improve symptoms. We have assumed that lavage alone would not be repeated. Since a 'biologics' licence was granted to Genzyme a number of randomised controlled trials have been launched and these give some indication of the treatments that might be adopted for treating cartilage defects. A list of these trials obtained from Genzyme's UK representative is shown later in this report. Three of the listed studies compare ACT with a marrow stimulation technique, two include debridement as one of the treatment arms, and two compare ACT with a periosseal flap (described in, Table 1, page 15, under 'grafting mesenchymal cells').

Figure 2 - A clinical decision pathway for the treatment of cartilage defects



TKR: Total knee replacement. * These include mosaicplasty, mesenchymal grafts, paste grafts, woven carbon fibre implants or osteochondral allografts (Table 1, page 26).

Table 1 - Treatment options for cartilage defects in knee joints

Method	Description and purpose
Knee washout (or lavage)	Either by a percutaneous route or at arthroscopy. The aim is to remove intra-articular debris, potentially harmful enzymes and to reduce inflammatory reactions ²⁹ .
Arthroscopic debridement	Includes a variety of local procedures but usually refers to removal of loose cartilage tissue surrounding a cartilage defect and is usually accompanied by a knee washout ³⁰ .
Marrow stimulation techniques	Includes 'abrasion arthroplasty', sub-chondral drilling, microfracture, and 'spongialization'. These techniques are applied to full thickness, or near full thickness, cartilage defects in which sub-chondral bone is visible. Defects are debrided and the sub-chondral bone is breached in various ways to allow access for bone marrow cells. The aim is to allow colonisation of a cartilage defect by precursor cells and initiate repair. In 'abrasion arthroplasty' the base of a cartilage defect is abraded with a motor driven burr to create superficial defects in subchondral bone ³¹ . Similarly, marrow cells may be exposed by drilling or picking sub-chondral bone, or more radically, sub-chondral may be resected ('spongialization'), exposing cancellous bone (or the spongiosa of bone), providing free access for bone marrow cells ³² .
Grafting mesenchymal cells	Some tissues such as periosteal cells (a delicate layer adjacent to, and overlying, bone) and perichondrium (a layer of cells around ribs) have a capacity for producing cartilage. These tissues may be grafted into knee cartilage defects with the aim of inducing repair ^{33,34} .
Woven carbon fibre grafts	Man-made carbon fibre discs, or other materials such as silicon and collagen, may be used to fill-in cartilage surface defects ³⁵ .
Mosaicplasty	Cylinders of normal cartilage and bone (~4.5 mm in diameter), from 'non weight bearing' areas of an affected knee are removed and placed into cartilage defects at a single surgical procedure. These are known as autografts and a patchwork is formed in repairing a cartilage defect, ensuring that the normal contours of cartilage are matched ³⁶ . This procedure is restricted to defects smaller than 2 cm ² in diameter and is not recommended in those with established OA ³⁷ .
Osteochondral grafts	Grafts of mature cartilage, with a supporting layer of bone (2-10 mm thick), fresh or frozen, and obtained from a donor (allografts). More commonly, used to treat cartilage injuries where there is need to restore bone, rather than isolated cartilage defects ³⁸ .
Paste grafts	A newly described technique in which cartilage and bone harvested from a non-weight bearing area of an affected knee, formed into a paste, and packed into a cartilage defect ³⁹ .
Autologous chondrocyte transplantation (ACT)	Autografts of cartilage, are taken from non-weight bearing areas of an affected knee during arthroscopic surgery. Grafts of 2-300 mg, an area of approximately 0.5 x 1-cm, are treated in a laboratory to expand the resident cell population (chondrocytes) for 3-5 weeks, and transplanted into cartilage defects at a second operation, requiring arthrotomy. To retain transplanted cells in a cartilage defect, cultured chondrocytes, in the form of a cell suspension, are injected beneath a specially created periosteal patch. Periosteal tissue is obtained from the proximal tibia at the second operation and cells are sealed with fibrin.

2.5 Current Service Provision

Most treatments for cartilage defects in a knee joint (Table 1, page 26) can be carried out at arthroscopy. Genzyme promotes chondrocyte transplantation through its tissue repair section CarticelSM, and has trained a number of orthopaedic surgeons in the techniques of chondrocyte transplantation. Worldwide 583 surgeons contribute patient information to a database maintained by Genzyme Tissue Repair⁴⁰. The majority of these surgeons are based in the US and Germany and 12 are based in England. Specific surgical skills are required for this technique. The agencies providing a service for chondrocyte transplantation require skills in the culture of cartilage cells in a laboratory, to an appropriate standard. Currently this service is also being offered by Verigen Transplantation Services Limited, through a facility in Copenhagen, and by a biotechnology firm Co-don for the German market⁴¹. In addition, in-house methods for chondrocyte culture, for use in human transplants, have been developed, and are in use, at The Robert Jones and Agnes Hunt Orthopaedic Hospital in Oswestry and a facility in East Grinstead. Research in Oswestry has been supported by a grant from the NHS Research and Development Section of the West Midlands and surgeons report that one procedure per week is carried out currently⁴². In Birmingham, nine procedures have been carried out in the past 2 years by one surgeon⁴³. Genzyme's representatives estimate, that a group of 20 surgeons in the UK, with a special interest in this area, see up to 20 patients suitable for ACT per annum.

3 Methods

3.1 Search strategy

The search for available evidence required two main strategies. First, an exhaustive search was made for all human studies, without language restriction, in which patients were treated with autologous chondrocyte transplantation. Sources such as the Cochrane Library and databases available through the website for the NHS Centre for Reviews and Dissemination (CRD)⁴⁴ including the Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Research Register, the National Economic Evaluation Database (NEED), and the Health Technology Assessment database (HTA) were searched. In addition, searches of the Medline, BIDS, and Embase databases were conducted, using an array of search terms in various combinations (

Table 2, page 29). The citation lists of all suitable reports were examined for other relevant publications.

Further reports on chondrocyte transplantation were sought by correspondence from surgeons who had an interest in this area and from some authors of prominent publications, and other researchers. Contacts were made, and meetings held, with Medical Representatives from Genzyme Tissue Repair and Verigen Transplantation Services Limited. Both Pharmaceutical agencies promote their services for chondrocyte culture and provide surgical training to interested surgeons. All abstracts from the 2nd International Cartilage Repair Society (ICRS) meeting held in Boston 1998 were obtained from these contacts. Abstracts from the American Association of Orthopaedic Surgeons for 1998 and 1999 were searched using the indexing term 'cartilage'. Abstracts of other recent international meetings, however, were not reviewed. Annual reports of the Cartilage Repair Registry, maintained by Genzyme Tissue Repair, were obtained and permission to include data from these reports has been obtained from Genzyme.

Table 2 - Terms and strategies used in Medline, Embase and BIDs searches

Arthroscopy	Chondral adj20 damage	Knee
Articular cartilage	Chondral adj20 defect\$	Knee injury
Athletic injuries	Chondral fracture	Knee disease
Cartilage cell	Chondral adj20 lesion\$	Knee joint
Cartilage adj20 damage	Chondropathy	Microfracture*
Cartilage adj20 defect	Chondrocytes	Osteochondritis dissecans
Cartilage graft	Chondrocyte implantation or chondrocyte transplantation	Osteochondral fracture
Cartilage adj20 injur\$	Drill\$*	Prognosis
Cartilage adj20 lesion\$	Implantation	Periost\$ adj20 flap*
Cell transplantation	Joint diseases	Transplantation, autologous

A second requirement for this review was to identify studies in which other methods of treating cartilage defects were used. For this purpose, and for pragmatic reasons, searches were confined to English language publications but the search strategy was otherwise unchanged. It should be noted that the search strategy in either case did not include the term ‘osteoarthritis’, or related terms, because the focus of this report is on chondrocyte transplantation, and established OA is regarded as a contraindication for ACT. It is possible however that by avoiding the search term osteoarthritis we missed reports on the treatment of early OA, which may have served as a comparator for ACT.

A limited search using the MeSH terms ‘knee’ or ‘knee injuries’ and ‘quality of life’ was conducted, in Medline, to aid the economic evaluation. A more exhaustive search was not conducted. We reasoned that the strategy described above and our professional links would identify all studies relevant to ACT, especially since cost is of particular concern. Any study with cost data in relation to ACT was obtained. Cost information was sought from the contracts department of the Royal Orthopaedic Hospital in Birmingham and from biotechnology firms promoting ACT, as well as from contacts at the Robert Jones and Agnes Hunt Orthopaedic Hospital in Oswestry. Further cost information was obtained from a study of MRI for knee disorders⁴⁵ which sought charges from 19 NHS Trusts and included costs for arthroscopy (daycase and inpatient).

3.2 Criteria for study inclusion

3.2.1 ACT

Any study, in any patient group, in which ACT was used, was included provided patient outcome data was available. This included data from a patient registry maintained by Genzyme Tissue Repair⁴⁶. Studies not reporting patient outcome data, for example studies that reported histological or radiographic data alone, were excluded. The most recent, or most complete, report was used if data from the same source was available in multiple publications.

Care was taken, where there were multiple publications of the same data, to ensure that the maximum possible numbers of patients were included and that follow-up duration was maximised.

3.2.2 Comparator treatments

Exclusion criteria, for studies in which treatments other than ACT were used are shown in Table 3, page 30. Osteochondral allograft transplantation was excluded as this treatment is most commonly used for those with cartilage defects involving a significant element of bony damage⁴⁷, and is not widely available because of difficulties in procuring and storing suitable material⁴⁸. Patients with 'anterior knee pain', 'patellofemoral pain syndrome', 'chondromalacia patellae' were excluded as this is a very heterogeneous group of patients in whom there is considerable uncertainty regarding treatment⁴⁹, although many patients with this disorder have patella cartilage damage⁵⁰. These exclusions, again, were adopted for pragmatic reasons since other methods for treating cartilage defects are not the focus of this report, but have been included to provide a context in which ACT should be viewed.

Table 3 - Exclusion criteria for comparator treatments for ACT

Studies of less than 25 subjects	Studies of patients with anterior knee pain syndromes
Studies published as abstracts only	Studies of patients with osteoarthritis (see introduction)
Foreign language publications	Studies lacking patient centred outcome data
Studies of osteochondral allograft transplantation (or shell allografts).	

3.3 Assessment of quality

Most studies consisted of descriptive case series or cohorts of patients without historical or concurrent controls. Since ACT represents a novel and expensive technology it is unlikely that many patients were excluded from published reports because of a failure to identify treated individuals or as a result of substantial loss to follow-up. For the purposes of this report studies were classified as 'A' if clinical outcomes included patient input before and after surgery, 'B' if patient input was available only after surgery, 'C' if only clinician or radiographic evaluation was provided without any patient input. One reviewer applied this simple scheme.

3.4 Data extraction

Patient outcome, which is central to the question addressed by this review, was abstracted by two reviewers from all relevant studies on ACT, using a specifically designed form. The data extraction form was piloted extensively before being applied. Discrepancies in data extraction were resolved by discussion or repeated independent checking of extracted data, until there was consensus. Foreign language publications were screened using the English language abstract if available or, were sent to professional contacts who were experienced at data extraction. Data from a selection of important comparator studies was also extracted by two reviewers to ensure consistency.

Data for many variables that may influence outcome for patients with cartilage defects was extracted. For example the site and size of a lesion, the subjects' age, length of follow-up, concomitant injuries, duration of symptoms preceding surgical intervention, the nature and extent of previous interventions, and the aetiology of a lesion. Data on global outcome was

given special emphasis and where possible these were expressed as a dichotomous variable, i.e. good or bad (if necessary by inference) in order to allow comparison between studies.

Length of follow-up, an important factor in assessing outcome, was recorded as the minimum length of follow-up not mean length of follow-up (unless the former was not available). Data on 'second-look' arthroscopy, where some treated patients were examined at a follow-up arthroscopy were included with the aim of identifying whether macroscopic appearance was regarded as acceptable or not. Histology of cartilage biopsies was available for small numbers of patients only. Although such data is of biological importance there is uncertainty about the relationship of histological appearances to clinical outcome. For these reasons histological descriptions of transplanted tissue were not extracted.

3.5 Data analysis

An initial attempt was made to express outcome data as an 'effect size' in order to allow comparisons between studies. However the data proved to be uninformative since most outcome data in these case series when presented as effect size, as defined by Kazis and colleagues⁵¹, showed a value greater than 1.0 suggesting a large effect of treatment. It is unlikely that some of the outcome indices such as the Lysolm score for knee function (see Appendix 2, page 79) can be regarded as continuous variables, which is a pre-requisite for calculation of effect size. This raised further uncertainty about the utility of effect size for this report and further attempts to create an index that allowed comparison of studies was abandoned.

4 Results

4.1 Autologous chondrocyte transplantation

A search of databases revealed very few studies on ACT and the largest sources of patient outcome data were found through contacts with pharmaceutical representatives and personal contacts with researchers in the field. In all, 37 pertinent studies or reports on chondrocyte transplantation were found. Of the twenty four excluded articles, fifteen were reviews, editorials or news features, eight reports had data duplicated or the reports were superseded by data from more recent sources, and in two cases there was no relevant data. A list of excluded studies, with reasons for exclusion, is shown in Appendix 1, page 75. Of the twelve studies from which data was extracted four had been published, at least partially. Seven were available in abstract form only. One was a voluntary patient registry maintained by Genzyme Tissue Repair, updated annually, and one, unpublished report, was currently being reviewed for publication. One study contained data on costs and a further unpublished document reported on financial benefits of ACT⁵². Six randomised clinical trials of ACT versus other interventions, which are currently underway, were identified and these are listed in Table 4, page 32.

Table 4 - Randomised Controlled Trials currently in progress*

1	300 patients. Multi-centre study based in US. 150 to receive ACT Carticel SM (Genzyme Tissue repair), 150 drilling / microfracture
2	80 patients. Multi-centre study based in US. 40 to receive periosteal graft without chondrocytes, 40 ACT Carticel SM (Genzyme Tissue repair).
3	60 patients. Malmoe University, Sweden. 20 periosteal graft without chondrocytes, 20 ACT (in-house technique), 20 debridement.
4	60 patients. Gothenburg, Sweden (Dr Matts Brittberg). 30 drilling with periosteal flap with or without ACT.
5	80 patients. Norwegian study (Dr Gunnar Knutsen), 40 ACT, 40 microfracture.
6	Multi-centre study Denmark (Dr Uffe Joergensen). Comparison of ACT, debridement and osteochondral graft (mosaicplasty) if lesions less than 2 cm ² .
* Source Sarah McGinn Carticel SM Project Manager UK, Genzyme Tissue Repair	

4.2 Other interventions for cartilage defects

A number of review articles, animal studies, studies of aetiology, studies concerned with classification of cartilage defects, studies of other sorts of knee injuries, studies concerned with technical aspects of tissue preservation and particularly, studies concerned with diagnostic tests such as MRI and arthroscopy, were scanned. Only an approximate record of articles and abstracts examined is available. Of the excluded reports, fifteen concerned osteochondral allografts which was judged to be an inappropriate comparator for ACT (see *Comparator treatments*, above). Twenty-five excluded reports, which are frequently cited in discussions of ACT, are shown in Appendix 1, page 75, along with the primary reason for exclusion.

4.3 Description of ACT studies and quality issues

All included studies were case series and detailed data is shown in Table 5, page 35. It appears likely, although not certain, that studies were describing a consecutive case series. All studies lacked a control group and, to date, relatively few patients have been followed for an adequate period of time (> 2 years). A further drawback of the studies identified was selection bias (how and why a particular individual was selected for ACT), and especially performance bias (greater care and attention being devoted to other aspects of patient care such as physical therapy or psychological needs, in those who receive ACT).

Two key reports, on the basis of the number of patients treated and followed for at least 2 years, were identified (Peterson et al⁵³ and the Cartilage Repair Registry maintained by Genzyme Tissue Repair). The results from these two reports are described in detail below and selected studies for comparator interventions are described in a later section. A summary of key data from studies with patients followed for 2 or more years is shown in Table 7, page 55.

4.3.1 Cartilage Repair Registry, Genzyme Tissue Repair (1999)

This is a voluntary registry. One obvious hazard of a voluntary database is that surgeons with poor results cease or decline to contribute data thus biasing results. It is unclear how many surgeons, who utilise the services of Genzyme Tissue Repair for treating cartilage defects, *do not* contribute data to the registry.

The current report provides data on over a thousand patients with a mean age of 35 years

(range 15-55 years). Nearly a third of knee problems arose from sporting activity and approximately a quarter each from falls or from daily activity. How long patients had had symptoms before ACT is unclear. However, 49% of patients had been treated with debridement and lavage in the 5 years before ACT and 28% by a marrow stimulation technique. The average size of defect was 4.3 cm² and 76% of defects were of full thickness. Many patients had additional procedures either at chondrocyte implantation or during cartilage harvesting. For example, approximately two-thirds had a further debridement, one in five had meniscus surgery, and one in ten ligament reconstruction.

Outcome, as judged by patients, was graded as good or excellent by 77% of 473 patients at one year and by 72% of 225 patients at two years following ACT. Specific assessments of knee pain and knee swelling also showed substantial improvements. During the follow-up period 'clinically relevant adverse events' occurred in 9.9% of patients, and 8.6% of patients required at least one further surgical procedure, usually by use of an arthroscope. The requirement for additional surgery increased with increasing follow-up. Additional procedures included lavage, removal of loose bodies, debridement or lysis of intra-articular adhesions. Treatment failure was defined as the need for a further procedure for the same defect in those with persistence or recurrence of symptoms; or if there was complete delamination or removal of the graft. Treatment failure occurred in 1.5% of cases at 1 year, 3.2% at 2 years and 4.7% at 3 years. Increased post-operative knee pain was noted by 1% of patients and 0.3% experienced a deep venous thrombosis or pulmonary embolism.

4.3.2 Peterson & colleagues⁵³

This case series describes up to 101 patients with an average age of 30 years. Twenty-one patients sustained injuries that were clearly related to sport. Most were twisting knee injuries. Patients had had symptoms for a mean of 4 years prior to ACT and approximately 83% of patients had undergone at least one previous surgical procedure. Details of the latter are not available but procedures included debridement, lavage, and marrow stimulation techniques. The average defect size was 4.3 cm² and all cartilage defects were of full thickness. Additional procedures, at the time of ACT, included ligament repair for 16% of patients. Details of other procedures such as meniscectomy, or meniscus repair, however, are not provided. The authors state that the technique of treating patellar lesions was modified with experience. Patients with patellar defects are described as receiving 'more radical debridement', in addition to 'patellar realignment when necessary' after initial experiences.

Outcomes have been reported in various sub-groups, depending on the site of cartilage loss. Overall, clinicians judged that 71% of patients had a good or excellent response compared with a fair or poor response in 25% of cases. Post-operative arthroscopic appearances were described as acceptable in 57% of cases. A further surgical procedure (requiring at least an arthroscopy) was carried out in approximately 21 cases (21%) and 7% (7/101) of grafts failed. Examination of sub-groups indicates that clinicians judge the outcome to be more favourable in those with defects in the femoral condyles (88% good or excellent) than patellar defects (59% good or excellent).

Table 5 - Summary data of included studies on autologous chondrocyte transplantation

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	<u>Clinical outcomes</u> Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Ratin g
<p>Burkhart A, et al. Abstract. ICRS, Boston, 1998.</p> <p><u>Intervention:</u> ACT</p> <p>7 patients</p>	<p>Undefined.</p> <p>Patient series</p> <p>Size: range 4-8 cm²</p>	<p>33 years</p> <p>100%</p> <p>3 months</p>	<p>Lysolm score (100=best, 0=worst) Pre-op 81, post-op 91</p> <p>2nd look Arthroscopy: 100% acceptable (inferred)</p>	<p>None reported.</p>	<p>A</p>
<p>Carticel Cartilage Repair Registry, Genzyme Tissue Repair. Vol. 5, Jan 1999.</p> <p>993 patients</p> <p><u>Intervention:</u> 100% ACT plus:-</p> <p>77% other procedures e.g. meniscus surgery 16%, ligament reconstruction 6%, debridement & lavage 69%, fragment reattachment or removal 14%.</p>	<p>Total defects 1269, MFC 61%, LFC 18%, patella 7.4%, trochlea 12.5%, tibia 0.9%</p> <p>Voluntary patient registry</p> <p>4.6cm² (1269 defects -all patients)</p> <p>Symptom duration not stated.</p> <p>Previous interventions: debridement & lavage 49%, abrasion or drilling or microfracture 28%, menisectomy 23%, 'primary cartilage treatment' 59%</p>	<p>35 years</p> <p>76%</p> <p>1 year data (485 patients)</p>	<p>Clinician Global assessment Good/Excellent 78% (379/484), Fair / Poor 22% (105/484)</p> <p>Patient Global assessment Good/Excellent 77% (364/473), Fair/ Poor 23% (109/473)</p> <p>OTHER OUTCOME SCALES</p> <p><u>Pre-op(SD)</u> <u>Post-op</u> <u>p value</u></p> <p><i>Clinician global</i> 3.5 (1.4) 6.2 <0.001 (2 poor, 10 excellent)</p> <p><i>Patient global</i> 3.2 (1.5) 5.7 <0.001 (2 poor, 10 excellent)</p> <p><i>Pain</i> 2.9 (2.1) 5.7 <0.001 (0 severe, 10 normal)</p> <p><i>Knee gives way fully</i> 6.8 (3.4) 8.4 <0.001 (0 severe, 10 normal)</p> <p><i>Knee swelling</i> 4.2 (2.8) 7.0 <0.001 (0 severe, 10 normal)</p>	<p>Reported for whole group of 1,896 patients in registry.</p> <p>'Treatment failure' 1.5% (cumulative treatment failure 4.7% at 3 years) 'Clinically relevant' adverse events: 9.9% <u>At least one further surgical procedure</u> 8.6% (re-implantation, further cartilage procedure, knee replacement or patellectomy 1.3%) Adhesions, hypertrophic change or loose body 5.2% Detachment, delamination, or periosteal tear: 2.4% Haematoma, synovitis, or effusion: 1.4% Superficial wound infection, cellulitis, or lymphangitis: 0.7% Infection of bone graft, donor site, pin tract, avascular necrosis, or joint infection: 0.3% DVT, pulmonary embolus: 0.3% Increased knee pain: 1%</p>	<p>A</p>

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	<u>Clinical outcomes</u> Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating																																												
Carticel Cartilage Repair Registry, Genzyme Tissue Repair. Volume 5, January 1999. 2 year data Up to 226 patients		2 year data	Clinician Global assessment Good/Excellent 77% (173/226), Fair / Poor 23% (53/226) Patient Global assessment Good/Excellent 72% (162/225), Fair/ Poor 28% (63/225) <u>Other outcome scales</u> <table border="0"> <tr> <td></td> <td><u>Pre-op(SD)</u></td> <td><u>Post-op</u></td> <td><u>p value</u></td> </tr> <tr> <td><i>Clinician global</i></td> <td>3.4 (1.2)</td> <td>6.3</td> <td><0.001</td> </tr> <tr> <td>(2 poor, 10 excellent)</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Patient global</i></td> <td>3.2 (1.4)</td> <td>5.8</td> <td><0.001</td> </tr> <tr> <td>(2 poor, 10 excellent)</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Pain</i></td> <td>3.2 (2.1)</td> <td>5.9</td> <td><0.001</td> </tr> <tr> <td>(0 severe, 10 normal)</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Knee gives way fully</i></td> <td>6.3 (3.6)</td> <td>8.0</td> <td><0.001</td> </tr> <tr> <td>(0 severe, 10 normal)</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Knee swelling</i></td> <td>4.2 (2.8)</td> <td>6.9</td> <td><0.001</td> </tr> <tr> <td>(0 severe, 10 normal)</td> <td></td> <td></td> <td></td> </tr> </table>		<u>Pre-op(SD)</u>	<u>Post-op</u>	<u>p value</u>	<i>Clinician global</i>	3.4 (1.2)	6.3	<0.001	(2 poor, 10 excellent)				<i>Patient global</i>	3.2 (1.4)	5.8	<0.001	(2 poor, 10 excellent)				<i>Pain</i>	3.2 (2.1)	5.9	<0.001	(0 severe, 10 normal)				<i>Knee gives way fully</i>	6.3 (3.6)	8.0	<0.001	(0 severe, 10 normal)				<i>Knee swelling</i>	4.2 (2.8)	6.9	<0.001	(0 severe, 10 normal)				See above. <u>Data specific for 2 years shown below.</u> Increased knee pain 1.7% Re-operation procedures Arthroscopic procedures including debridement, lavage, loose body removal, partial implant removal, synovectomy, meniscus procedures, ligament repair and plica resection ≥ 11.4% (display 16) Total knee replacement 0.5% Osteochondral autograft 0.3% Drilling 0.4% Repeat ACT 0.4% Abrasion arthroplasty 0.1%	A
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Georgoulis A, et al. Abstract ICRS, Boston 1998. 12 patients	Site: MFC 8/12 (67%), LFC 4/12(33%), intercondylar notch 1/12 (8%), OCD 1/12 Consecutive patients Defect size: 4.5cm ²	28 years 6 months	Improvement of pain: 100% Return to work at 6 months: 100%	Post-operative effusion 1/12 (8%)	C																																												

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<p>Gillogly SD, et al. J Orthop Sports Phy Ther 1998;28:241-51.</p> <p>Up to 41 patients</p> <p><u>Intervention:</u> 100%ACT plus:- all procedures 19/41 (46%), ACL repair 7/41 (17%), transposition of tibial tubercle 12/41 (29%), high tibial osteotomy (2%), meniscus surgery 1/41 (2%)</p>	<p>MFC 27/53 (51%), LFC 12/53 (23%), trochlea 7/53(13%), patella 6/53(11%), 6/41 (15%) OCD.</p> <p>Patient series.</p> <p>Defect size: 5.7 cm²</p> <p>Previous interventions: 29/41 (71%) 'surgery directed at chondral injury'</p>	<p>36 years</p> <p>1 year follow-up for 25 patients</p>	<p>Overall patient / clinician (Cincinnati): Good to excellent: 22/25 (88%)</p> <p>Outcome scores</p> <table border="1" data-bbox="873 521 1415 943"> <thead> <tr> <th>value</th> <th>Pre-op</th> <th>Post-op</th> <th>p</th> </tr> </thead> <tbody> <tr> <td><i>Cincinnati- clinician</i> <0.001</td> <td>3.3</td> <td>6.8</td> <td></td> </tr> <tr> <td><i>Cincinnati- patient</i> <0.001</td> <td>3.2</td> <td>6.7</td> <td></td> </tr> <tr> <td>(1=worst, 10=best)</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Pain (0-10)</i> <0.001</td> <td>3.9</td> <td>7.8</td> <td></td> </tr> <tr> <td><i>Swelling (0-10)</i> <0.001</td> <td>4.3</td> <td>8.1</td> <td></td> </tr> <tr> <td><i>Knee Society Score</i> <0.001</td> <td>67</td> <td>89</td> <td></td> </tr> <tr> <td>(0-100)</td> <td></td> <td></td> <td></td> </tr> <tr> <td><i>Sports score(0-100)</i> <0.001</td> <td>38</td> <td>66</td> <td></td> </tr> </tbody> </table>	value	Pre-op	Post-op	p	<i>Cincinnati- clinician</i> <0.001	3.3	6.8		<i>Cincinnati- patient</i> <0.001	3.2	6.7		(1=worst, 10=best)				<i>Pain (0-10)</i> <0.001	3.9	7.8		<i>Swelling (0-10)</i> <0.001	4.3	8.1		<i>Knee Society Score</i> <0.001	67	89		(0-100)				<i>Sports score(0-100)</i> <0.001	38	66		<p>None reported</p> <p>Need for further surgery 3/41 (7%). Debridement for hypertrophy (1), arthroscopic lysis of adhesions (2).</p>	A
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<i>Pain (0-10)</i> <0.001	3.9	7.8																																							
<i>Swelling (0-10)</i> <0.001	4.3	8.1																																							
<i>Knee Society Score</i> <0.001	67	89																																							
(0-100)																																									
<i>Sports score(0-100)</i> <0.001	38	66																																							
<p>Hart JAL, et al. Abstract ICRS, Boston, 1998.</p> <p>16 patients</p> <p><u>Intervention:</u> 100% ACT + 64% other 'biomechanical procedures'.</p>	<p>Total defects 42, patella 40%, trochlea 17%, femoral condyles 52%, tibia condyles 7%</p> <p>Patient series.</p>	<p>Age <45 yrs</p> <p>9 months</p>	<p>100% improved pain – clinician assessment 100% improved function – clinician assessment</p> <p>2nd look arthroscopy: 7/17 (53%) lesions in 13 patients acceptable appearance. Synovitis improved in 100%</p>	<p>1 patient with effusion at 9 months</p> <p>Need for further surgery 1/16 (6%)</p>	C																																				

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	<u>Clinical outcomes</u> Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating															
<p>Koh JL, et al. Abstract, ICRS, Boston 1998.</p> <p>14 patients</p> <p>Intervention: 100% ACT; additional procedures unclear</p>	<p>MFC 8 (54%), trochlea 5, patella 1</p> <p>Patient series.</p> <p>Defect Size: 2.5cm²</p> <p>Previous interventions: 13/14 (93%). Including debridement, meniscectomy, ligament reconstruction (2/14), drilling or abrasion (5/14), mosaicplasty (1/14)</p>	<p>35 years</p> <p>3 months</p>	<p>Improved pain 7/14 (50%) - clinician assessment? Improved activity 3/14 (21%) – clinician assessment? Activity worse or same 11/14 (79%)</p> <p>Overall clinician rating (0=worst, 10=best) Pre-op 3.1, Post-op 4.8</p> <p>Global clinician rating: 8/14 (57%) improved, 6/14 (43%) worse</p>	<p>None reported.</p> <p>Need for further surgery 7/14 (50%)</p> <p>2nd look arthroscopy assume for therapeutic reasons: all unacceptable.</p>	C															
<p>Löhnert J, et al. Arthroscopie 1999⁵⁴.</p> <p>Total 60 patients but outcome data on 20 patients only</p> <p>ACT, other interventions not stated</p>	<p>MFC 44, LFC 16, patello-femoral joint 6. 17 OCD lesions.</p> <p>Patient series</p> <p>Defect size: 4 cm²</p> <p>Previous interventions: not stated</p>	<p>35 years (13-68)</p> <p>-</p> <p>>1 year for 20 patients (mean 15 months)</p>	<p>Cincinatti (global): Pre-op 6 fair, 14 bad; Post-op 9 very good and 11 good i.e. 100% good/v. good.</p> <table border="1" data-bbox="863 998 1425 1161"> <thead> <tr> <th></th> <th>Pre-op</th> <th>post-op</th> </tr> </thead> <tbody> <tr> <td>Lysolm</td> <td>21.4</td> <td>91.3</td> </tr> <tr> <td>Hospital for Special Surgery</td> <td>44</td> <td>90.5</td> </tr> <tr> <td>Tegner</td> <td>1.5</td> <td>4.5</td> </tr> <tr> <td>DGKKT score (0 worst, 100 best)</td> <td>22.3</td> <td>90.5</td> </tr> </tbody> </table> <p>MRI scans 6 months post-op 100% defects filled</p>		Pre-op	post-op	Lysolm	21.4	91.3	Hospital for Special Surgery	44	90.5	Tegner	1.5	4.5	DGKKT score (0 worst, 100 best)	22.3	90.5	<p>No DVT or infections. 3/60 patients had knee effusions, one requiring aspiration</p>	A
	Pre-op	post-op																		
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Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	<u>Clinical outcomes</u> Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating
<p>McKeon BP, et al. Abstract, ICRS, Boston 1998.</p> <p>23 patients</p> <p><u>Intervention:</u> 100% ACT + 4/23 (17%) other procedures e.g. 1 tibial osteotomy, 1 ligament repair, 2 hardware removal</p>	<p>MFC 15, trochlea 7, LFC 6, patella 3, tibia 1</p> <p>Patient series</p> <p>Defect size: 3.8 cm²</p> <p>Previous interventions: 2.4 procedures on average per patient – not specified</p>	<p>38 years</p> <p>100% full thickness</p> <p>Mean: 13 months</p>	<p>Improved pain 100% - clinician assessment Improved function 100% - clinician assessment</p>	<p>None reported</p> <p>2nd look arthroscopy 3/23: all acceptable</p>	C
<p>Minas T. Am J Orthop 1998⁵⁵ & Minas T, presentation abstract American Academy of Orthopedic Surgeons, 1998.</p> <p>Up to 70 but mostly 44 patients' data</p> <p><u>Intervention:</u> 100% ACT + other procedures not stated.</p>	<p>MFC 38/87 lesions (44%), LFC 11 (13%), patella 15 (17%), tibial plateau 5 (6%)</p> <p>14/44 (32%) patients with OA (osteophytes or <50% joint space narrowing)</p> <p>Patient series.</p> <p>Defect size: 5.5 cm²</p> <p>Previous interventions: 87% previous knee surgery, 55% prior abrasion, drilling, microfracture, or perichondrial graft</p>	<p>36 years</p> <p>-</p> <p>1 year</p>	<p><u>Outcome Scores</u> Pre-op Post-op p value</p> <p>SF-36</p> <p>Physical scale 33.3 41.5 <0.05 Mental 49.3 51.6 0.65 Social function 57.1 81.3 <0.001 <i>Knee Society</i> 114 141 <0.001 <i>WOMAC*</i> 35 24 <0.05</p> <p>5 of 8 SF-36 component scales showed statistically significant increase at 1 year after surgery (p<0.05). These were physical function, role-physical, bodily pain, vitality, and social function.</p> <p>Direct in-hospital cost \$17,607 - \$38,400 (mean \$26,769, SD \$4888). Cost per QALY range \$4701 - \$9403. 10% change in combined SF-36 produced no change in cost per QALY.</p> <p>Patient Global assessment 72% (n=44?) improved, 28% same or worse. 'Efficacy maintained at 24 months.</p>	<p>'Treatment failure' 5/70 (7%)</p> <p>Periosteal hypertrophy 10%</p> <p>'Incomplete integration' 11%</p> <p>Need for further surgery 26/70 (37%) – usually treated at arthroscopy</p>	A

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	<u>Clinical outcomes</u> Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating																		
<p>Peterson L, et al, submitted 1999. Lindahl A, et al, submitted 1999.</p> <p>Up to 101 patients</p> <p><u>Intervention:</u> ACT + ligament repair 16/101 (16%), other procedures included debridement of chondromalacia, patellar realignment</p>	<p>MFC and LFC 41/94 (44%), OCD 18/94 (19%), patella 19/94 (20%), multiple 16/94 (17%).</p> <p>Consecutive patient series</p> <p>Retrospective case review and prospective clinical assessments including patients evaluations</p> <p>Duration of symptoms 4.0 years (range 0.4-44)</p> <p>Defect size: 4.3 cm²</p>	<p>30 years</p> <p>100%</p> <p>Follow-up: ≥2 years</p>	<p><u>Overall Clinician Assessment</u> <u>Good or excellent</u> 93/101 (71%) for whole group, 52/59 (88%) for femoral condyle and OCD sub-group, 20/34 (59%) for patella and multiple lesion sub-group <u>Fair or worse</u> 25/101 (25%) for whole group, 7/59 (12%) for femoral condyle and OCD sub-group, 14/34 (41%) for patella and multiple lesion sub-group.</p> <p><u>Patient overall assessment</u> Improved 73/93 (79%) whole group, 50/59 (85%) for femoral condyle and OCD sub-group, 23/34 (68%) for patella and multiple lesion sub-group.</p> <p><u>Outcomes scores for femoral condyle and OCD group only n=59 (calculated)</u></p> <table border="1" data-bbox="873 865 1415 1185"> <thead> <tr> <th></th> <th><u>Pre- op</u></th> <th><u>Post-op</u></th> </tr> </thead> <tbody> <tr> <td>Lysolm (0 worst, 100 best) (p<0.005)</td> <td>47</td> <td>80</td> </tr> <tr> <td>Cincinnati (0 worst, 100 best) (p<0.005)</td> <td>32</td> <td>58</td> </tr> <tr> <td>Noyes (0 worst, 10 best) (p<0.001)</td> <td>1.4</td> <td>8.2</td> </tr> <tr> <td>Brittberg-Peterson (0 best, 130 worst) (p<0.005)</td> <td>75</td> <td>23</td> </tr> <tr> <td>Wallgren-Tegner (0 worst, 15 best)</td> <td>6.7</td> <td>9</td> </tr> </tbody> </table> <p>Second-look arthroscopy (>2 yr post surgery) for femoral condyle and OCD group (n=53): acceptable 57%, unacceptable 23%</p> <p>From Lindahl et al (sub-group of 57 patients - unclear how they were selected).</p> <p>Costs in the 10 years prior to ACT (incl. surgical,</p>		<u>Pre- op</u>	<u>Post-op</u>	Lysolm (0 worst, 100 best) (p<0.005)	47	80	Cincinnati (0 worst, 100 best) (p<0.005)	32	58	Noyes (0 worst, 10 best) (p<0.001)	1.4	8.2	Brittberg-Peterson (0 best, 130 worst) (p<0.005)	75	23	Wallgren-Tegner (0 worst, 15 best)	6.7	9	<p>Further surgery 21/101 (21%) Haemarthrosis 2% Superficial infection 3% Fever 1% Graft failure 7/101 (7%)</p>	<p>A</p>
	<u>Pre- op</u>	<u>Post-op</u>																					
Lysolm (0 worst, 100 best) (p<0.005)	47	80																					
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			<p>for 2 procedures, rehabilitation, and absence from work): \$128,682.</p> <p>Post-ACT costs projected over 10 years, assuming only 0.3 surgical procedures: \$2,070.</p> <p>Authors estimate real cost saving of \$88,146 for an average patient.</p>		
<p>Scorrano A. Abstract, ICRS, Boston 1998.</p> <p>25 patients</p> <p><u>Intervention:</u> ACT.</p> <p>Other procedures not stated, use of pins for ACT.</p>	<p>MFC 19, LFC 3, patella 5.</p> <p>Defect size: 9.8 cm²</p>	<p>37 years</p>	<p>Cincinnati rating: 24/25 (96%) good/ excellent, 1/25 (4%) fair</p>	<p>No adverse events</p> <p>No data on need for further surgery</p>	<p>B</p>

F/U: follow up. ICRS: International Cartilage Repair Society. *WOMAC: Western Ontario and McMaster University Osteoarthritis Index (Bellamy N, et al. J Rheum 1988;15:1833-40).

4.4 Studies of other treatment options for cartilage defects

The impact of other interventions for knee cartilage defects is also reported primarily as case series. These case series include very different sorts of patients. For example Blevins and colleagues⁵⁶ only report on athletes, all with full thickness cartilage defects, whilst in other reports only 10% of patients had full thickness cartilage loss. Patient age varies between a mean of 26 years and over 50 years in these series, and some studies clearly include a proportion of patients with well-established OA⁵⁷. There was also heterogeneity in the sorts of treatments used and types of injuries / knee problems treated. Thus there is a real concern that like is not being compared with like, particularly since factors such as disease of the anterior cruciate ligament⁵⁸ or of menisci⁵⁹ may influence outcome.

Despite these reservations some key messages emerge. First, it is evident that there is no established standard therapy for cartilage defects against which ACT can be compared. Second, few of the reported interventions has been evaluated in controlled studies. For example, Hubbard's randomised open study is the only included report with a group of concurrent controls. This study reports on older individuals with cartilage defects, of uncertain severity, on the medial femoral condyle (a site believed to have a favourable prognosis). Hubbard reported that 59% (19/32) of patients who had their cartilage defect debrided were pain free after 5 years compared with 12% (3/26) of those treated by knee lavage only³⁰.

Short term outcomes, of up to 3 years, are mostly favourable for a variety of treatments. This includes marrow stimulation techniques (drilling and abrasion), removal or re-fixation of loose fragments, mosaicplasty, and even those who do not receive a specific surgical intervention, other than diagnostic arthroscopy. In most cases good or excellent results are reported for between 69% to 97% of patients. Patients treated with rib perichondrial grafts however did not do as well, with 38% having a good or excellent outcome 14 months after treatment⁶⁰. Short term outcomes are likely to give a false impression of the effectiveness of surgical interventions. This is because cartilage defects repair by forming fibrocartilage. This tissue is mechanically inferior to hyaline cartilage and is unlikely to be durable⁵. But, the relationship between the type of the underlying tissue repair and symptoms is unclear.

Few reports describe follow up beyond 3 years and most are older publications of patients with OCD. Linden found that most adults with OCD develop OA, when followed for at least 25 years. Aichroth, followed 105 patients for an average of 13 years and found that 63% had good or excellent function, with or without surgical intervention⁶¹. A quarter of patients developed moderate or severe OA. These reports suggest that follow up beyond 20 years may be required before drawing firm conclusions about the outcome of any intervention. It is uncertain whether outcomes reported for OCD can be compared directly with outcomes for other types of cartilage defect. However OCD is regarded as an indication for ACT. Most studies of OCD include relatively young patients and such individuals have a greater capacity for cartilage repair¹⁰. The only long term follow up study of patients with a cartilage defect, diagnosed at arthroscopy, is a report by Maletius and Messner⁵⁹. In this study of 42 patients 62% had good or excellent outcomes after at least 12 years follow-up although only 12% of patients had a full thickness cartilage defect.

Mosaicplasty appears to give exceptional results, for example 95% of patients returned to normal activity⁶². This technique is only feasible in patients with smaller cartilage defects. Therefore patients who received ACT, may not be comparable with those who are treated by

mosaicplasty. Both treatments use normal cartilage from within an abnormal joint to repair the damaged area. This results in a new, surgically created, cartilage defect. The areas from which such cartilage is removed are regarded as unimportant for weight-bearing and knee function. However a recent report, in cadavers, shows that these areas are subject to significant contact pressure⁶³. Thus there are anxieties about the potential long-term impact of surgically created cartilage defects. A final and important criticism of the studies described in this section is that, in general, adverse effects of surgery are not described adequately. Indeed studies of ACT provide a more complete description of adverse effects.

Table 6 - Alternative treatments for cartilage defects: Summary of included studies

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Ratin g																												
Aichroth P, JBJS (Br) 1971⁶¹. 105 patients with OCD No surgery 26/105 (25%), arthrotomy 12 (11%), drilling 7 (7%), excision of fragment 22 (21%), fixation 9 (9%), patellectomy 7/126 (6%)	85% MFC, 15% LFC, 5/105 (5%) patella Patient series – response from 105 of 150 contacted - Previous interventions: Most initially managed by conservative treatment.	18 years 100% Average follow-up: 13 years	80/126 (63%) knees good or excellent 46/126 (37%) moderate or poor Radiographic osteoarthritis (moderate or severe): 32/126 (25%)	- 17/126 (13%)	C																												
Blevins FT, et al. 1998³⁶. 140 recreational athletes. Data on a further 48 athletes not available. Intervention: Microfracture + Meniscal surg. - up to 30% Ligament repair- up to 35% Continuous passive motion, home use 55%	MFC 97/188 (52%), LFC 46 (25%), tibia 63 (34%), patella 17 (9%) Patient series Size (mean) 2.9 cm ² Symptoms: 68 months	38 years 100% 1 year	<table border="0"> <tr> <td></td> <td><u>Pre- (SD)</u></td> <td><u>Post-op</u></td> <td><u>p value</u></td> </tr> <tr> <td>Activities of daily</td> <td>5.8 (3.3)</td> <td>7.8</td> <td><0.05</td> </tr> <tr> <td>(0 low, 10 high)</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Pain (1 none, 4 severe)</td> <td>3.2 (1.1)</td> <td>2.2</td> <td><0.05</td> </tr> <tr> <td>Giving way (1-4)</td> <td>2.4 (1.1)</td> <td>1.4</td> <td><0.05</td> </tr> <tr> <td>Swelling (1-4)</td> <td>2.7 (1.2)</td> <td>1.8</td> <td><0.05</td> </tr> <tr> <td>Locking (1-4)</td> <td>1.7 (1.2)</td> <td>1.2</td> <td><0.05</td> </tr> </table> 2 nd look arthroscopy: ≥35% unacceptable		<u>Pre- (SD)</u>	<u>Post-op</u>	<u>p value</u>	Activities of daily	5.8 (3.3)	7.8	<0.05	(0 low, 10 high)				Pain (1 none, 4 severe)	3.2 (1.1)	2.2	<0.05	Giving way (1-4)	2.4 (1.1)	1.4	<0.05	Swelling (1-4)	2.7 (1.2)	1.8	<0.05	Locking (1-4)	1.7 (1.2)	1.2	<0.05	Not reported.	A
	<u>Pre- (SD)</u>	<u>Post-op</u>	<u>p value</u>																														
Activities of daily	5.8 (3.3)	7.8	<0.05																														
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Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating
<p>Blevins FT, et al. Orthopaedics 1998³⁶.</p> <p>38 professional, semi-professional, Olympic or National level. Data on 10 others not available.</p> <p>Intervention: Microfracture + meniscal surgery (up to 31%), ligament repair (up to 39%)</p>	<p>MFC 17/48 (35%), LFC 18/48 (38%), tibia 7/48 (14%), patella 4/48 (8%)</p> <p>Patient series</p> <p>Size (mean): 2.3 cm²</p> <p>Symptoms: 28 months</p>	<p>~26 years</p> <p>100%</p> <p>1 year</p>	<p>24/31 (77%) returned to pre-op activity level. 17 did not return questionnaire (i.e. actual total 48).</p> <p>Pre- (SD) Post-op p value Activities of daily 6.1 (3.8) 8.7 <0.05 (0 low, 10 high) Pain (1 none, 4 severe) 3.1 (1.0) 2.0 <0.05 Swelling (1-4) 3.1 (1.2) 1.7 <0.05 Locking (1-4) 1.8 (1.1) 1.0 <0.05</p> <p>2nd look arthroscopy: ≥8% unacceptable</p>	<p>Not reported</p>	<p>A</p>
<p>Boumeester SJM, et al. Int Orthop 1997⁶⁰.</p> <p>88 patients</p> <p>Rib perichondrial graft + Meniscectomy or anterior cruciate repair 13/88 15%</p>	<p>96 defects including OCD. MFC 43 (45%), LFC 5 (5%), patella 50 (52%).</p> <p>35/81 (43%) grade 1 OA, 5/81 (6%) grade 3 or 4 OA.</p> <p>Patient series</p> <p>Size: range 0.3 to 20.5 cm²</p> <p>Symptoms: not stated</p> <p>Previous interventions: Drilling 12/88, OCD lesions (14%)</p>	<p>31 years</p> <p>14 months</p>	<p>Hospital for Special Surgery Score (85-100=excellent or good, 75-85=fair, <75=poor)</p> <p>Good/ excellent – 38% Fair – 8% Poor / Re-operation or failure – 55%</p>	<p>None reported except for failure i.e. poor outcome / re-operation or failure 55%</p>	<p>B</p>

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating
<p>Drongowski RA, et al. Arthroscopy 1994⁵⁸.</p> <p>99 patients with ACL injury (49 with cartilage lesions, 50 without). Concomitant injuries: meniscus (lateral and medial) and collateral ligament</p> <p>Intervention: No surgery except 'diagnostic arthroscopy' and drilling in 5/49 (10%)</p>	<p>Numbers unclear, 32 cartilage lesions reported. 19 (59%) LFC, 13 (41%) tibial plateau, 4 (13%) MFC</p> <p>Consecutive patients with ACL injury choosing conservative treatment. 107 patients of whom 8 lost to follow-up</p> <p>Previous interventions: none</p>	<p>-</p> <p>12/49 24%</p> <p>Mean follow-up: 52 months</p>	<p><u>Cartilage injury?</u> Yes No</p> <p>No limit activity 5/49 (10%) 15/50 (30%) Some limit 24/49 (49%) 25/50 (50%) Severe limit 20/49 (41%) 10/50 (20%)</p> <p>Ability to jog Cartilage injury: 35/49(71%) patients were jogging before injury, 21/49 (43%) after injury p<0.05 No cartilage injury: 39/50 (78%) patients were jogging before injury, post-injury 32/50 (64%).</p>	<p>None reported</p>	<p>B</p>
<p>Dzioba RB. Arthroscopy 1988⁶⁴.</p> <p>65 patients</p> <p>Intervention: vertical excision of diseased tissue + drilling of subchondral plate</p>	<p>MFC:LFC = 4:1, 3/65 (5%) tibial</p> <p>Patient series.</p> <p>34 lesions (52%) small (<1cm), 22 (34%) medium (1-3 cm), 9 (14%) large (>3cm)</p> <p>Less than 3 weeks: 45/65 (69%)</p> <p>Previous interventions: Not stated</p>	<p>Age: 16-59 years</p> <p>7/65 (13%) full thickness</p> <p>13 months</p>	<p>Good 69%, Fair 3%, Poor 28%</p> <p>2nd look arthroscopy (46 knees): Acceptable appearance 30/46 65%, unacceptable 16/46 35%</p>	<p>None reported</p>	<p>C</p>

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating
<p>Ewing JW, Voto SJ, Arthroscopy 1988⁶⁵.</p> <p>29 patients</p> <p>Intervention: All had arthroscopic surgery. 25/29 (86%) excision with drilling or abrasion. Loose body removal only 4/29 (14%). Partial meniscectomy 5/29 (17%)</p>	<p>MFC 19, LFC 10. All lesions OCD.</p> <p>Patient series</p> <p>-</p> <p>Greater than 2 years 10/29 (34%) remainder less than 2 years.</p> <p>Previous interventions not stated.</p>	<p>25 years</p> <p>100%</p> <p>11 months</p>	<p>Lysolm: Excellent / Good 21/29 (72%) Fair or poor 8/29 (38%)</p> <p>Patient opinion as above.</p> <p>2nd look arthroscopy 10 patients none healed.</p>	<p>Adverse events not reported. 2/29 (7%) re-abraded.</p>	<p>B</p>
<p>Green JP, JBJS (Br) 1966⁶⁶.</p> <p>40 patients.</p> <p>Intervention: Surgery 32/43 (74%) knees including trimming and fragment removal (12/43; 28%), loose body removal (10/43; 23%), exploration of knee (3//43; 7%), drilling (2/43; 5%), re-fixation of graft (5/43; 12%).</p> <p>No surgery 11/43 (26%).</p>	<p>MFC 37, LFC 6 All lesions were OCD.</p> <p>Patient series.</p> <p>-</p> <p>4.6 years (but 41% within 1 year)</p> <p>Previous interventions; not stated</p>	<p>17 years</p> <p>100%</p> <p>>1year (mean 7 years)</p>	<p>Good or excellent 36/40 (90%) knees Unsatisfactory 4/40 (10%)</p> <p>Radiographic OA: 11/40 (28%)</p>		<p>C</p>

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Ratin g
<p>Hangody L, et al. Orthopaedics 1998³⁶.</p> <p>57 patients</p> <p>Intervention: Mosaicplasty 100% plus post-operative drug treatment with NSAIDs</p> <p>Concomitant procedures: ACL reconstruction 28%, Meniscal resection or reconstruction 33%, Debridement 8%, femoral-tibial alignment 13%</p>	<p>MFC 19/57 (33%), LFC 16 (28%), Patella 7 (12%), OCD 15 (26%)</p> <p>Patient series</p> <p>Defect size: 1-8.5 cm²</p> <p>Duration of symptoms: 5 months (mean)</p> <p>-</p>	<p>31 years</p> <p>~100% full thickness</p> <p>3 years</p>	<p>Hospital for Special Surgery Score post-op: 90.7</p> <p>Return to normal activity: 54/57 (95%)</p> <p>2nd look arthroscopy (19 patients): acceptable 84%, unacceptable 16%</p>	<p>Haemarthrosis 2/57 3.5%</p> <p>Need for further surgery: 2/57 (3.5%)</p>	B
<p>Homminga GN, et al. JBJS (Br) 1990⁶⁷.</p> <p>25 patients</p> <p>Costal perichondrial graft fixed with fibrin glue. 2/25 (8%): repair of ACL.</p>	<p>Site: MFC 15, LFC 3, patella 11, intercondylar groove, 1. 7/25 (28%) osteophytes on radiographs.</p> <p>Patient series</p> <p>Defect size (taken as graft size): 2.1 cm² (1-5)</p> <p>Symptoms pre-op: 37 months</p> <p>Previous interventions: 11/25 removal of degenerative cartilage, drilling, or lateral release</p>	<p>31 years</p> <p>-</p> <p>1 year</p>	<p>Ranawat Knee Score (0=worst, 100=best): Pre-op 73 (SD 9), Post-op 90, p<0.001</p> <p>Completely free of symptoms and resumption of work/sport: 18/25 (72%)</p> <p>2nd look arthroscopy (3-12 months post-op): Acceptable appearance 27/30 grafts (90%), unacceptable 10%</p>	<p>Not reported.</p>	A

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating
<p>Hubbard MJS. JBJS (Br) 1996³⁰.</p> <p>Up to 76 patients (36 lavage only, 40 debridement and lavage)</p> <p>No other interventions reported.</p>	<p>Site: 100% MFC</p> <p>Randomised open study without blinded assessment</p> <p>Symptoms pre-op: > 1 year</p> <p>Previous surgery: none reported.</p>	<p>50 year – debridement group 57 years – lavage</p> <p>-</p> <p>1 year & 5 year data</p>	<p>1 year 5 years</p> <p>Debridement Pain 8/40 (20%) 13/32 (41%) No pain 32/40 (80%) 19/32 (59%) Lavage Pain 31/36 (86%) 23/26 (88%) No pain 5/36 (14%) 3/26 (12%)</p> <p>Debridement vs Lavage, p<0.05 at 1 year</p> <p><u>Modified Lysohm</u> (0=worst, 70=best, score for laxity excluded – a priori exclusion of laxity) Scores: Pre-op 1 year 5 years Debridm. 35 (n=40) 55 (n=40) 48 (n=32) Lavage 35 (n=36) 39 (n=36) 38 (n=26)</p>	<p>Not reported</p>	<p>A</p>
<p>Hughston JC, et al. JBJS (Am) 1984⁶⁸.</p> <p>83 patients (95 knees). 22 knees no surgery, 73 knees surgery i.e. removal of bone fragment, or drilling and pinning of fragment</p> <p>Concomitant procedures: Surgical group: 3/73 (4%) patellar realignment, 5/73 (7%) meniscectomy</p>	<p>78 MFC, 17 LFC: All OCD.</p> <p>Patient series of 94 patients of whom 11 lost to follow-up.</p> <p>Previous meniscectomy in 4/95 (4%) other details not available.</p>	<p>No surgery: 17yr Surgery: 20 yr</p> <p>100%</p> <p>> 2 years</p>	<p>Clinician global:</p> <p>No surgery: 18/22 (82%) good or excellent, 4/22 (18%) fair or poor</p> <p>Surgery: 56/73 (77%) good or excellent, 17/73 (23%) fair or poor</p> <p>Size of defect in outcome categories: Good/ Excellent 4.2 cm² (1-9.6) Fair 4.7 cm² (2.8-9) Poor or fail 8.2 cm² (3.2-12)</p> <p>Follow-up > 10 years (23 knees, surgical and non-surgical combined) 74% good or excellent</p>	<p>Further surgery (probable minimum) 4/95 (4%).</p>	<p>C</p>

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating
<p>Katz JN, et al. J Rheum 1992⁶⁹.</p> <p>36 patients (sub-group of 105 undergoing meniscectomy)</p> <p>Treatment of cartilage lesion not recorded. 100% meniscectomy, 14% of 105 patients ACL reconstruction.</p>	<p>No details</p> <p>Patient series: 34/105 (32%) with radiographic osteoarthritis</p> <p>Previous surgery in 22% of 105 patients</p>	<p>-</p> <p>Greater than or equal to grade 3 Outerbridge.</p> <p>-</p>	<p>Lysolm (<77; considered unsatisfactory) 44%</p> <p>Lysolm (>77 i.e. satisfactory) 56%</p> <p>SF-36: 24.5 for those with cartilage damage 15 if no cartilage damage</p>	<p>-</p>	<p>B</p>
<p>Linden B. JBJS (Am) 1977¹⁰.</p> <p>58 patients (18 children i.e. open epiphysis & 40 adults); 95 joints.</p> <p>30/95 (32%) no treatment, 8/95 (8%) plaster cast, 57/95 (60%) arthrotomy and removal of loose fragment.</p>	<p>All OCD.</p> <p>Case series.</p> <p>-</p> <p>-</p> <p>-</p>	<p>24 years for whole group.</p> <p>29 years adults (n=40, 44 joints); 13 years children (n=18, 23 joints).</p> <p>100%</p> <p>All patients (mean) 32 years (min. ~25)</p>	<p>Greater than 'some pain' 26/34 joints (76%; 32 patients)</p> <p>Physical dysfunction. Minimum 21/34 (62%) joints; moderate 10/34 (29%); severe 1/34 (3%).</p> <p>Angular deformity of joint: 23/34 (68%).</p> <p>Abnormal range of motion 21/34 (62%).</p> <p>Radiographic OA Of some degree: 45/76 (59%); mild 16/76 (21%), severe 29/76 (38%), none 31/76 (41%).</p>	<p>Not reported</p>	<p>C</p>

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating																
<p>Maletius W, Messner K. Am J Sports Med 1996.</p> <p>42 patients with cartilage lesions (21 had meniscectomy, 21 did not) to assess impact of partial meniscectomy on outcome.</p> <p>Exclusions: - Ligament injury - Previous surgery</p>	<p>30 MFC, 12 LFC (15 MFC & 6 LFC each group)</p> <p>Retrospective case-control study.</p> <p>Pre-op symptoms: mean 13 months</p> <p>Size: '>1/3rd of diameter of width of condyle</p> <p>None</p>	<p>29 years</p> <p>5/42 (12%)</p> <p>12 years</p>	<p>Clinician global (based on Lysholm cut-off 84 points): Excellent/good): 62%. Poor / fair: 38%</p> <p>Lysholm (mean), post-op: 87 for whole group, 85 (SD 13) for meniscectomy group; 88 (SD 10) for no meniscectomy group. p value =NS.</p> <p>Return to pre-injury activity level: 24%</p> <p><u>Tegner score</u> (10=competitive sport, 0=unable to work): Pre-op 6 (recreational sport), follow-up 4, all patients, no difference with meniscectomy.</p> <p><u>Osteoarthritis on X-ray</u></p> <table border="1"> <thead> <tr> <th></th> <th><u>All patients</u> n=42</th> <th><u>meniscectomy</u> n=21</th> <th><u>no menis.</u> n=21</th> </tr> </thead> <tbody> <tr> <td>None</td> <td>9 (21%)</td> <td>3 (14%)</td> <td>6 (28%)</td> </tr> <tr> <td>>Some</td> <td>33 (79%)</td> <td>18 (86%)</td> <td>15 (71%)</td> </tr> <tr> <td>Severe</td> <td>10 (24%)</td> <td>9(43%)</td> <td>1 (5%)</td> </tr> </tbody> </table>		<u>All patients</u> n=42	<u>meniscectomy</u> n=21	<u>no menis.</u> n=21	None	9 (21%)	3 (14%)	6 (28%)	>Some	33 (79%)	18 (86%)	15 (71%)	Severe	10 (24%)	9(43%)	1 (5%)	<p>Knee effusions 2/42 (5%)</p> <p>Further surgery all patients 10/42 (24%), chondral damage group 3/21 (14%), meniscectomy 7/21 (33%).</p>	B
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<p>Mayer G, Seidlein H. Arch Orthop Trauma Surg 1988⁷⁰.</p> <p>50 patients.</p> <p>Interventions: Debridement. Others: - Removal of bone and cartilage fragments 16 (32%) Drilling 24 (48%) Extra-articular sub chondral levelling 3 (6%) - Fragment re-fixation 11 (22%)</p>	<p>Various lesions including 10 with osteochondral fragments on plain X-rays</p> <p>Patient series. Included 9 meniscal injuries, 2 cruciate ligament deficiency.</p> <p>Pre-op symptoms: <1 month</p> <p>None</p>	<p>26 years</p> <p>-</p> <p>1 year</p>	<p>Clinician global: good or excellent: 60%</p>	<p>None reported</p> <p>-</p>	C																

Study Interventions Patients Concomitant procedures	Site(s) Study type Mean defect size Duration of symptoms pre-op Previous interventions	Mean age % full thickness cartilage loss Minimum follow-up	Clinical outcomes Global scores Outcome indices 2 nd Look arthroscopy Economic data	Adverse events Need for at least one further surgical procedure	Rating																											
<ul style="list-style-type: none"> - Tibial tuberosity displacement 21 (42%) - Soft tissue. surgery 12 (24%) 																																
<p>Noyes FR, Barber-Westin. Am J Sports Med 1997⁷¹.</p> <p>53 patients</p> <p>Cartilage intervention: 13/53 (25%) drilling or abrasion arthroplasty, 22/53 (42%) 'chondroplasty of unstable cartilage'</p> <p>100% ACL reconstruction 21/53 40% partial meniscectomy (medial or lateral) 24/53 patients, 45%, meniscal repair</p>	<p>Medial-tibio-femoral 33, Lat-tibio-femoral 22, patello-femoral 16</p> <p>">15mm area"</p> <p>Sub-group with cartilage lesions identified from prospective study of ACL repair</p> <p>Pre-op symptoms: 90 (range 5-340) months</p> <p>Previous interventions: total 37/53 (70%) patients; 90 procedures ACL reconstruction 10/53 (19%) Debridement 36/53 (68%) Meniscectomy or meniscal repair 40/90 (44%) Other 4/90 (4%)</p>	<p>32 years</p> <p>38% (others had 'extensive fissuring and fragmentation)</p> <p>22 months</p>	<p><u>Patient global:</u> Improved (good/excellent or normal) 85% Same or worse (poor or fair) 16%</p> <p><u>Patient - pain:</u> Improved 37/53 (70%) Same or worse 16/53 (30%)</p> <table border="0" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; border-bottom: 1px solid black;">(SD)</th> <th style="text-align: center; border-bottom: 1px solid black;">Pre-op (SD)</th> <th style="text-align: center; border-bottom: 1px solid black;">Post-op</th> </tr> </thead> <tbody> <tr> <td>Noyes (0 worst, 100 best)</td> <td style="text-align: center;">56 (8)</td> <td style="text-align: center;">86 (11)</td> </tr> <tr> <td>Overall patient rating</td> <td colspan="2" style="text-align: center;">3.2 (1.5)</td> </tr> <tr> <td></td> <td colspan="2" style="text-align: center;">6.9 (2)</td> </tr> <tr> <td></td> <td colspan="2" style="text-align: center;">(1-10)</td> </tr> <tr> <td>Pain with ADL</td> <td style="text-align: center;">34%</td> <td style="text-align: center;">6%</td> </tr> <tr> <td>Gives way (part/full)</td> <td style="text-align: center;">43%</td> <td style="text-align: center;">2%</td> </tr> <tr> <td>Swelling with ADL</td> <td style="text-align: center;">26%</td> <td style="text-align: center;">4%</td> </tr> <tr> <td>Able to do modr. sport</td> <td style="text-align: center;">13%</td> <td style="text-align: center;">38%</td> </tr> </tbody> </table> <p>2nd look arthroscopy 24, after >7 months, 6 new lesions</p>	(SD)	Pre-op (SD)	Post-op	Noyes (0 worst, 100 best)	56 (8)	86 (11)	Overall patient rating	3.2 (1.5)			6.9 (2)			(1-10)		Pain with ADL	34%	6%	Gives way (part/full)	43%	2%	Swelling with ADL	26%	4%	Able to do modr. sport	13%	38%	<p>Saphenous neuralgia 2/40 (5%)</p> <p>Further surgery 26/40 (65%), removal of screw - appears to relate to ACL repair</p>	<p>A</p>
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<p>Pongor P, et al. Biomaterials 1992⁷².</p> <p>96 patients</p> <p>Intervention: Debridement, woven carbon mesh or rods</p>	<p>8 OCD, 57 OA of patello-femoral or medial femoro-tibial joint, 31 chondromalacia</p> <p>Patient series</p> <p>-</p> <p>-</p> <p>-</p>	<p>39 years</p> <p>-</p> <p>9 months</p>	<p>Patient global evaluation: Excellent/Good 68/96 (71%) Fair / Poor 28/96 (29%)</p> <p>Modr./severe pain: Pre-op 80%, Post-op 39% Mild/No pain: Pre-op 20%, Post-op 61%</p> <p>Pain VAS (0=none, 10=worst). Pre-op 5.6 (retrospective judgement), Post-op 2.4</p> <p>Climbing stairs (no aids): Pre-op 34%, Post-op 61%</p> <p>Overall pain post-op: 76/96 (79%) improved, 20/96 (21%), no change or worse</p>	<p>Not reported</p>	<p>A</p>
<p>Takeda T, et al. J Orthop Sci 1997⁷³.</p> <p>129 patients with cartilage damage (260 overall)</p> <p>Patients selected from group who had ACL reconstruction <i>and</i> who had achieved excellent / satisfactory joint stability <i>and</i> full extension, <i>and</i> 135°, <i>and</i> came to follow-up. Treatment of cartilage lesions not recorded.</p>	<p>-</p> <p>Analysis of effect of mensical injury and cartilage damage on ability to return to sport</p> <p>-</p> <p>ACL reconstruction 100%</p>	<p>-</p> <p>No cartilage damage: 27%, Grade 1: 24%, grade 2: 41%, grade 3 (full thickness): 7.6%</p> <p>7 months</p>	<p><u>%returning to sports</u></p> <p>No cartilage damage 83% Grade 1 75% Grade 2 57% Grade 3 (full thickness) 59%</p>		<p>C</p>

F/U: follow up. ICRS: International Cartilage Repair Society. OCD: Osteochondritis dissecans. MFC: Medial femoral condyle. LFC: Lateral femoral condyle. TP: Tibial plateau.

4.5 Summary of effectiveness data

Data presented in the last two sections emphasises that patient characteristics are very variable. For instance, in many studies only a small proportion of patients have full thickness cartilage defects whilst in others all patients have full thickness defects. This creates uncertainty when comparing different studies. In addition it should be apparent that patients often receive multiple interventions not simply those that are the subject of any particular report. For example in Peterson and colleagues report of ACT, 16% of patients had a ligament repair. Substantial proportions of patients in other studies also undergo additional procedures such as tibial tubercle transfer and meniscus repair or removal. Finally an essential element in determining outcome of a procedure is the duration of follow-up. This is emphasised by the observational studies of OCD. Key studies reporting follow times of 2 or more years for ACT and alternative treatments are shown in Table 7, page 55. In summary, 71% to 77% of patients treated with ACT report a good or excellent outcome at two years whilst for comparator treatments this figure ranges between 10% and 95%. The wide range for comparator treatments may reflect patient heterogeneity rather than treatment effect.

Table 7 - Summary of key outcomes. Reports with follow-up of at least 2 years.

Study	Follow-up (years)*	Max. patients	Good or excellent outcome	<u>Need for ≥ 1 additional surgical procedure</u>
<i>ACT</i>				
Carticel Registry	≥ 2	226	77%	11.4% **
Peterson et al.	≥ 2	101	71%	21%
Other treatments(intervention)				
Aichroth (mixed)	13 [†]	105	63%	13%
Drongowski (arthroscopy \pm drilling)	4.3 [†]	99	10%	-
Hangody (mosaicplasty)	≥ 3	57	95%	3.5%
Hubbard (debridement)	5	32	59%	-
Hubbard (lavage)	5	26	12%	-
Hugston (mixed)	≥ 2	83	82%	$\geq 4\%$
Linden (mixed)	≥ 25	58	24%	-
Maletius (\pm menisectomy)	12	42	62%	24%
*Median unless indicated otherwise. [†] mean number of years. – indicates unreported data. ** Although the overall figure for re-operation is given as 8.6% this figure increases with time so that by 2 years 11.4% have had at least one operation and by 3 years this figure is 13.6%.				

5 Economic analysis

5.1 Economic analysis: methods

The economic analysis aims to synthesise the cost and the effectiveness evidence for ACT versus other procedures for the treatment of cartilage defects in knee joints. Where possible we have provided a cost-utility analysis (cost per QALY). Two time horizons were considered. First, from treatment to two year follow-up (the limit of the effectiveness evidence). Second, from treatment to ten year follow-up. It is clear from long-term follow-up studies, for example Linden (Table 7, page 55), that 2 years is an inadequate length of follow-up. It is possible therefore that clear differences between therapies might emerge with increased follow-up. This is biologically plausible if, with ACT, cartilage defects are replaced with hyaline cartilage that is durable and if with microfracture techniques, for example, cartilage defects are replaced by mechanically inferior fibrocartilage that fails in time. On these grounds and in order to capture a possible increased requirement for total knee replacement with comparator treatments, or conversely better outcomes with ACT⁷⁴, it was considered necessary to provide the longer time horizon. This was done despite inadequate long-term data. But, a projection allowed us to consider a sustained positive clinical effect of ACT and poor long-term durability of comparator treatments.

In conducting the economic analysis the clinical decision pathway, shown in Figure 2, page 25, was modified to capture likely current practice. Probabilities, outcomes and costs were then attached to these pathways to create a decision tree. The consequences of the interventions in terms of quality of life, have been estimated from measurements on the EuroQol instrument (EQ-5D) in patients with other knee disorders⁷⁵. This was necessary since no included study used a generic health status measure that could be converted into a quality adjusted life year (QALY) and an important goal of the economic analysis was to inform decisions about resource allocation.

Resource use has been viewed from the perspective of the NHS and not of individual patients or society. Any substantial economic impacts on society or on individuals are described in the text. Unit cost estimates were obtained from a variety of sources including published literature, data from the Royal Orthopaedic Hospital in Birmingham, a recent survey of 11 NHS Trusts⁴⁵ and unpublished Swedish data provided by Anders Lindahl⁵². Mean costs were calculated where data were available for comparable procedures. Where unit costs for particular procedures were not available costs of an equivalent procedure, with appropriate adjustments, were used. Where costs were available in older publications an adjustment was made for inflation by assuming a 5% compounded inflation rate. Both costs and effects are reported both undiscounted and discounted at 6%.

5.2 Summary of literature

Two reports have examined the economics of ACT. Neither study, however, compared ACT with any other treatment. Minas (Table 5, page 35) calculated direct in-hospital costs and estimated quality adjusted life years (QALYs) using the Short Form-36. He also assumed that all costs were incurred during the first year and concluded that ACT has a cost per QALY of \$6791 (£4303). It is unclear how a QALY is calculated in this report and it is also unclear how the 28% of patients who showed no improvement, or deteriorated, were considered. For example, the financial impact of further surgical interventions in these individuals do not

appear to be included. By contrast Lindahl and colleagues, in an unpublished report, compare work absenteeism and direct medical costs in the 10 years prior to ACT with the projected costs 10 years after ACT. Fifty-seven patients are included and costs of further surgery are considered. The authors calculate that ACT leads to a real cost saving of \$88,146 (£54,411). In sensitivity analyses the authors estimated that the threshold for equal costs occurred if the re-operation rate after ACT was 18% per annum, and if work absenteeism exceeded 28 days per annum.

5.3 Assumptions and decision tree

In order to make this evaluation as informative as possible an attempt has been made to extrapolate the available data to capture long term outcomes. The data is presented for 2 years and 10 years so that a possible requirement for total knee replacement (TKR) surgery is included in the analysis. There is a widespread but unproven perception that the costs of ACT might be offset if TKR is at least deferred to a later date⁵⁵. In order to include TKR in the decision tree, and to reflect clinical realities, the decision tree shown in Figure 2, page 25, was modified to that shown in Figure 3, page 61. This simplifies the decision choice; ACT versus any other surgical therapeutic option. It has been assumed since cartilage defects are most likely to be diagnosed at arthroscopy, that most individuals with a defect would undergo at least a knee lavage, but more likely would undergo debridement (see Hubbard, Table 6, page 45). The start point for the decision tree is therefore patients with symptomatic cartilage defect after debridement. In those with poor outcomes after debridement it is assumed that, for those in whom surgery is contemplated, the choice usually lies between a marrow stimulation technique, further debridement, mosaicplasty, carbon fibre implants, or ACT.

Life threatening adverse events of surgery such as severe infection and pulmonary embolism, have not been included in the decision analysis. This is justified on the grounds that such events are rare. They occurred, for example, in less than 1% of cases in the Cartilage Repair Registry. However, since ACT involves 2 surgical procedures, first to harvest cartilage and second for implantation after culture, compared with, say, a marrow stimulation technique, where only one procedure is performed, this represents a doubling of the risk of serious adverse events associated with surgery. Nevertheless many patients with symptomatic cartilage defects appear to undergo several surgical procedures with any therapeutic strategy. Therefore it is assumed that over 10 years the risk of a serious adverse events, such as pulmonary embolism, are approximately equal in the two main branches of the decision tree.

Table 8 - Estimated probabilities for outcomes shown in the decision tree

	<u>2 year</u>	<u>10 years</u>		
	<u>Base case</u>	<u>Base case</u>	<u>Worst</u>	<u>Best</u>
<i>ACT</i>				
Good outcome/no more surgery	0.75	0.75	0.6	0.8
Poor outcome/no more surgery	0.125	0.09	0.14	0.072
Poor outcome/more surgery/no TKR	0.12	0.12	0.19	0.096
Poor outcome/more surgery/TKR	0.005†	0.04	0.06	0.032
<i>Comparator</i>				
Good outcome/no more surgery	0.7	0.7	0.4	0.9
Poor outcome/no more surgery	0.12	0.06	0.12	0.02
Poor outcome/further surgery/no TKR	0.17	0.168	0.33	0.056
Poor outcome/further surgery/TKR	0.005*	0.072	0.14	0.024

† Data from Carticel Repair Registry. * No reliable data - therefore estimates are adopted from ACT.

Two-year analysis: ACT & Comparator treatments

Two-year economic analysis was based on clinical effectiveness data summarised in Table 7, page 55. Estimated probabilities are shown in Table 8, page 58. For ACT we have accepted that around 75% of patients have good outcomes at 2 years and we have assumed that approximately 12.5% of patients undergo further surgery (the figures for Peterson et al are 21% and for the Cartilage Repair Registry 11.4% at 2years). This assumption is at the lower end of the published range as the Cartilage Repair Registry has a considerably greater number of patients. For comparator treatments we have assumed that a slightly lesser percentage of patients do well at 2 years. We chose a figure of 70%. This assumption is based on data shown Table 8, page 58. With no clear rationale for calculating an average we have taken 70% to the base line value. This issue was addressed in sensitivity analysis.

In general included studies of comparator treatments have followed patients for longer periods and the range of good outcomes varies from 10% to 95% with follow-up times between 2 years and 25 years. We also assumed that of those receiving comparator treatments, and not doing well, a greater proportion of patients would undergo further surgery. We assumed that 17.5% of all patients undergoing surgery with comparator treatments would require additional surgery. Figures chosen on the need for TKR are based on data in the Cartilage Repair Registry which shows that 0.5% of patients treated with ACT required TKR. In the absence of similar data for comparator treatments we have accepted that TKR is required in a similar proportion of patients treated in other ways.

5.3.1 Ten-year analysis: ACT

We assumed that patients treated with ACT if they have done well at 2 years will continue to do well. Thus for the base case analysis (Table 8, page 58) we assumed that 75% of patients will remain well at 10 years. This assumption was tested in sensitivity analysis. A range of 60% to 80% of patients doing well was explored. For comparator treatments we have again

assumed that those doing well at 2-years remain well at 10 years but in sensitivity analysis we explore a wider range of 40% to 90% doing well based on effectiveness data in Table 7, page 55.

For the 10 year economic analysis the early annual surgical ‘failure’ rate (not all those with poor outcomes), from the Cartilage Repair Registry and Peterson and colleagues report, was used and projected forward in time to capture the possibility of TKR. It was assumed that all failures would have further surgery and that a proportion would need TKR in due course. Data from the Cartilage Repair Registry indicates a failure rate of 4.7% after 3 years (an average annual rate of 1.56%). Whether this rate is maintained year on year is unclear and it is possible that, after a period of time, the overall failure rate might plateau. Satisfactory biological repair with ACT requires some months and failures might be expected whilst hyaline cartilage is formed during the early months after surgery. For this reason, the failure rate might be expected to plateau with time. Peterson and colleagues, report a failure rate of 7% at 3 years (an average annual rate of 2.3%). Failures in their study occurred within 2 years and a greater proportion of failures arose during early experiences with ACT also suggesting a learning effect. Using figures from these two studies, and assuming that the failure rate is maintained year on year, over 10 years a failure rate of between 15.6% and 23% might be expected. Thus for the base case analysis we assumed that 16% might be regarded as failures at 10 years and that all these patients would be subjected to additional surgery. In sensitivity analysis we explored a range of 12% to 26% requiring additional surgery after ACT.

In assessing the requirement for TKR we assumed that all patients classified as failures of treatment would be considered for TKR. Data from the Cartilage Repair Registry shows that, of the 1896 patients treated with ACT, 0.2% at had TKR at 1 year, 0.5% at 2 years, and 1.9% at 3 years. For the base case analysis we assumed that the requirement for TKR might eventually plateau and estimated that 4% of patients might require TKR at 10 years. In sensitivity analysis we explored a range of 3.2% and 6.4% requiring TKR. We assumed that requirement for TKR would occur at the end of the 10 year time horizon. This was done for pragmatic reasons in order to simplify our analysis and modelling.

An additional concern when considering long term outcomes is that normal cartilage is removed from a diseased joint as a source of chondrocytes in ACT. Cartilage from these areas is subject to significant contact pressures⁶³. Removal of this normal tissue may have a detrimental effect. But, for the purposes of this analysis it has been assumed that there are no detrimental effects.

5.3.2 Ten-year analysis: Comparator treatments

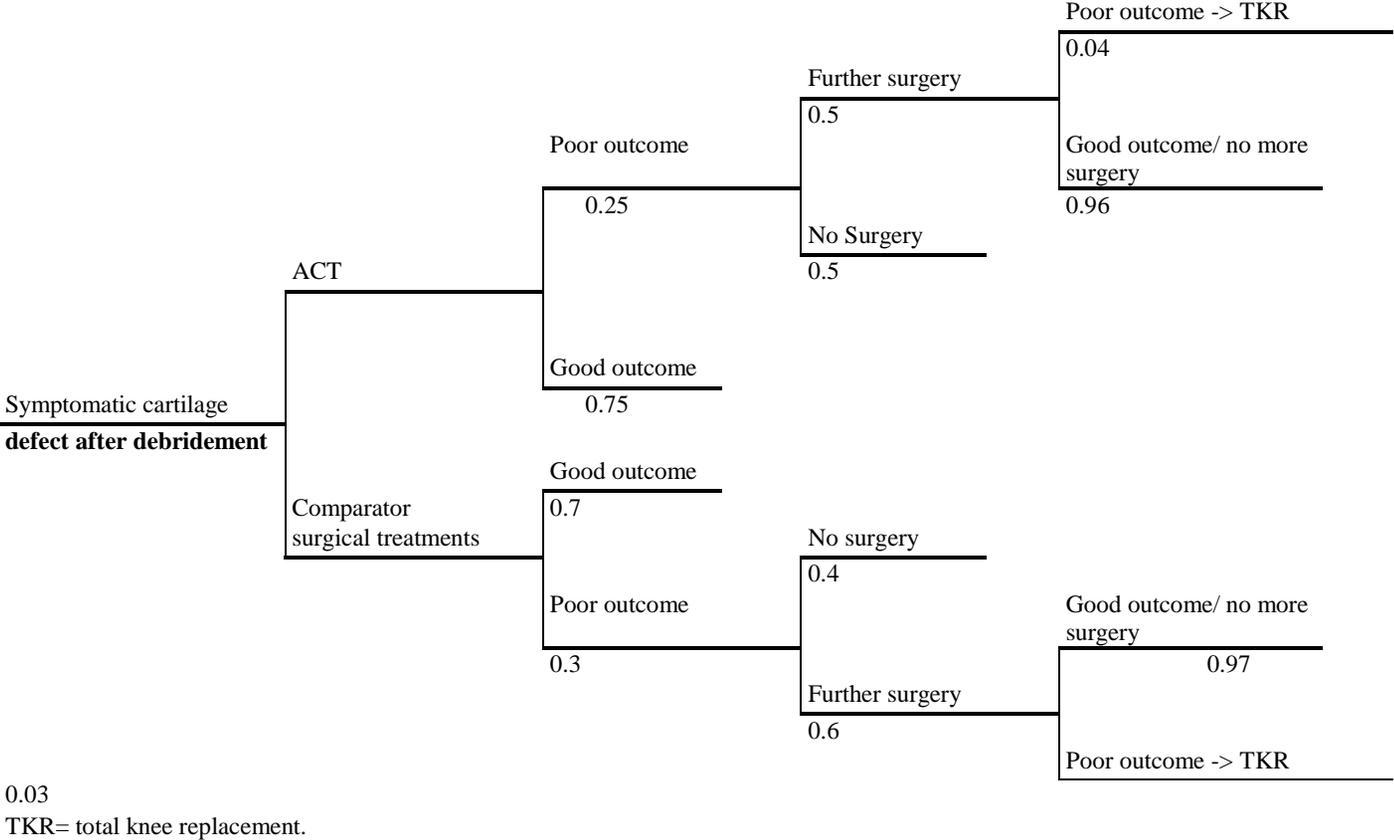
To estimate to 10-year follow-up, and particularly to try and understand the natural history of cartilage defects, it was necessary to rely on descriptive data from series of patients with OCD. Many series of OCD patients describe juveniles who are skeletally immature⁶¹. Since outcomes may be better in juveniles¹⁰, and as the average age of patients treated with ACT is between 30 and 35 years such series may not provide suitable data. Therefore, greater emphasis is given to series of patients that give details of outcomes in adults with OCD. Even this data may be unsuitable since the aetiology, and possibly the prognosis, of OCD may differ from that of other sorts of cartilage defects treated with ACT. However in the absence of other data, and since 19% of the patients described by Peterson and colleagues had OCD, we believe this is acceptable for estimating costs.

Long term follow-up of adults with OCD showed that 43% went on to develop ‘severe’ osteoarthritis after a minimum follow up of 25 years¹⁰. This is likely to be an underestimate

since many patients classified as having 'mild' OA on X-rays might today be classified as having more advanced disease. In another report of patients with cartilage defects 24% developed severe OA after a minimum follow-up of 12 years⁵⁹. Figures, from these two reports, yield an annual OA rate (if we regard the development of OA as a failure) of between 2 to 3.5% per annum, assuming a steady rate of failure. Thus after 10 years 20-35% of patients are estimated to have significant OA with a possible requirement for additional surgery. For base case analysis we assumed that 24% of patients would have had additional surgery after 10 years follow-up. This was based on the report by Maletius & Messner⁵⁹. Because of the uncertainty of effectiveness data we explored a wide range in sensitivity analysis (8% to 48%) based loosely on long-term follow studies of OCD.

We assumed that a greater proportion would undergo TKR than after ACT treatment. We chose a figure, in base case analysis, of 7.2% requiring TKR at 10 years. Sensitivity analysis explored a requirement for TKR in the range 2.4% to 14%.

Figure 3 - Decision tree used for economic analysis showing base case probabilities



5.4 Quality of life assumptions: Utilities

Only one report of ACT treatment included a generic health status measure (SF-36)⁵⁵. Unfortunately utilities for SF-36 data are not currently available and data cannot readily be expressed in terms of QALYs. Rather than creating a theoretical patient profile, utility values from a report of heterogeneous knee disorders were used⁷⁶. In this study utilities were available for patients who continued under hospital supervision with their knee disorder or were discharged from hospital, following an MRI. It was assumed that those who were discharged from hospital care had good outcomes and that the health utilities of such patients would equate to good outcomes following ACT. To ensure that these assumptions were justified SF-36 values in this study were compared with SF-36 values reported by Minas in his study of ACT⁵⁵. It was noted that patients treated with ACT had substantially lower scores on the SF36 in the physical functioning and pain domains, than patients who were discharged from hospital following MRI. This suggested that we had over-estimated health utilities following ACT treatment. However we also conducted a 'mapping' exercise using EQ-5D for patients with a successful outcome after ACT. We assumed, using the five domains of EQ-5D, that patients might experience no problems with mobility, no problems with self-care, some or no problems with usual activity, some pain or discomfort, and some or no anxiety or depression. This yielded health utilities in the range 0.689 to 0.796. The higher figure equates to that reported by patients who were discharged from hospital care after MRI. We therefore accepted the published value as being reasonable for those with good outcomes post ACT.

In estimating utilities for patients with a symptomatic cartilage lesion (the starting point of our decision tree) we assumed that patients with knee disorders who continue under hospital supervision following MRI would have similar utilities⁷⁵. Estimates of utilities, further assumptions and sources of estimates are shown in Table 9, page 65. To determine a utility score for those with more advanced disease, and where there is a poor long-term outcome after an intervention, data from a study of patients undergoing total knee arthroplasty are used to estimate an appropriate utility⁷⁶. A mapping exercise in this situation was unhelpful since it suggested that health utilities might range from -0.074 to 0.691¹. The health utilities obtained from estimates have been rank ordered and inspected to ensure that they are clinically sensible. For simplicity, utilities have been assessed for a particular outcome as a whole ('holistic method'⁷⁷).

Details of year on year estimates used to determine an overall utility value for a period of 10 years, following ACT or an alternative procedure, are shown in **Appendix 3**, page 81. In estimating year on year utility some assumptions about a change in utility with time have been made. For example, it is assumed that a good outcome following ACT is sustained for a 10 year period but that good outcomes following comparator treatments decline after 5 years by one standard deviation for 2 years and by two standard deviations for the final 3 years (using utility data shown in Table 9, page 65). This was done to allow for the possibility that tissue repair following comparator treatments may not be as durable as tissue formed following ACT.

¹ It was clear from this exercise that the EQ-5D instrument is very sensitive to severe pain, if a patient is reporting severe pain but no problems in the remaining domains, the QALY weight is 0.264. If the level of pain can be reduced to a moderate level then the score increases to 0.796.

5.5 Cost assumptions

Details of unit costs, available from national and local sources, are shown in Appendix 4 and Appendix 5. Where precise details of the cost of a procedure, for example the cost of further surgery to effect repair after ACT, are not available an estimate from individual items is made. A list of estimated mean costs for pathways in the decision analysis (with ranges) is shown in Table 10, page 69. Future costs, for example the cost of TKR, have been expressed as discounted values ('net present value'), using a rate of 6% per annum, and as an undiscounted value. ACT requires culture of chondrocytes in a laboratory before implantation. There is a risk of failure with this process, which may vary with different providers of this service. A report from Genzyme indicates that only 1 order out of 304 orders failed to meet release specifications⁷⁸. For the purposes of this decision analysis it has been assumed that no failures occur. It should be recognised however that failure to meet specifications means that, potentially, a patient is subjected to an additional arthroscopy for procuring more tissue. Similar data from other providers of a culture facility for chondrocytes are not published and it is not clear whether Genzymes' figures can be matched. It is also unclear whether all providers of chondrocyte culture facilities, especially those with cheaper in-house facilities, adhere to uniform biological safety standards. Inadequate laboratory standards might therefore compromise patient outcomes and increase risk.

Table 9 - Rank ordering of estimated utilities used for decision analysis using Euroqol 5-D

Outcome	Utility (SD)
Good outcome after ACT**	0.795 (0.18)
Good outcome after comparator treatments**	0.795 (0.18)
Symptomatic cartilage defect after debridement* (<u>starting point for decision analysis</u>)	0.643 (0.2)
Poor outcome after ACT not undergoing surgery	0.643
Poor outcome after comparator treatments not undergoing surgery	0.643
Poor outcome after ACT, receiving further surgery but not TKR†	0.615
Poor outcome after comparator treatments, receiving further surgery but not TKR	0.615
Poor outcome after ACT undergoing further surgery	0.443
Poor outcome after comparator treatments undergoing further surgery	0.443
Poor outcome after ACT, receiving surgery and proceeding to TKR	0.359 (range 0.13-0.75)
Poor outcome after comparator treatments, receiving surgery and proceeding to TKR	0.359 (range 0.13-0.75)
*based on knee MRI patients who continue to require hospital attention (Hollingworth). **based on Knee MRI patients who are discharged from hospital follow up after MRI scanning. # Assumed to be 1 sd worse off than those with symptomatic cartilage defects after debridement. † Assumed to be 1 sd worse off than those with a good outcome after ACT or comparator treatments.	

5.6 Results

5.6.1 Effectiveness

At 2 years follow-up there is no significant difference in effect between ACT and other treatments. Both treatment options approximately provide an expected 1.35 QALYs. Clinical effectiveness data (summarised in Table 7, page 55) shows that there is a great range of possible outcomes from 10% to 95% of patients experiencing a good or excellent outcome with comparator interventions, whilst the evidence for ACT is more stable at approximately 75% of patients experiencing a good or excellent outcome.

At 10 years follow-up (results summarised in Table 10, page 69) ACT provided an expected QALY score of 4.9 QALYS versus 4.1 QALYS for the comparator. This difference arose because we assumed that those treated with ACT had a more durable clinical response due to better tissue repair, compared with those receiving other treatments. Long term data is required to test this assumption.

5.6.2 Cost

At 2 years follow-up there is a substantial cost difference. The expected cost of ACT was £9,200 versus £1,600 for the comparator.

At 10 years follow-up the cost difference persisted. Expected cost of ACT was £10,400 versus £3000 for comparator treatments.

5.6.3 Cost-utility

At 2 years follow-up it was not possible to carry out a cost utility analysis as there is no difference in effect. A cost minimisation analysis which looks simply at the cost difference shows that ACT has an incremental cost of £7,600 for no gain in effectiveness.

At 10 years follow-up the base case analysis suggests an incremental (additional) cost per QALY gain of approximately £9,000.

5.6.4 Sensitivity analysis

In order to simplify decision analysis manipulation of probabilities, in sensitivity analysis, was focused on initial outcome following an intervention (based on study reports giving follow-up over 2 to 3 years) which then had an impact on later events (Figure 3, page 61). Thus good outcomes for ACT were explored in the range of 60-80% whilst good outcomes for comparator studies, accepting the caveats with regard to patient heterogeneity described above, were explored in the range of 40-90%. Such a wide range was considered for comparator studies in view of the poor quality of most reports and a serious concern about publication bias.

It was assumed that further surgical interventions, including TKR, would occur only in those with poor outcomes. The probability of TKR at 10 years, in the ACT treatment arm, was considered to lie between 3 and 6%. For comparator treatments this figure was 2.4% to 19.2%. These figures are comparable to those cited earlier for the risk of developing advanced OA. Changes in the costs of TKR and ACT were also considered in the sensitivity analysis. The base case cost for TKR was derived from the mean HRG cost from the 1998 NHS reference costs. The 25th (£3,800) and 75th percentile (£4,900) of this data was considered as a plausible best and worst case cost of TKR. For ACT there is much less guidance on the cost of the procedure. The base case cost for ACT is also assumed to be the worst case cost. The lowest cost estimate uses a low cost of cell cultivation of £2778 (as quoted for Verigen) and assumes that the procedure can be carried out in two arthroscopy procedures, giving a cost of £3,800. Alternative costs of £6,000 and £7,500 are also considered.

Sensitivity analysis is summarised in Table 11, page 70. For the 2 year model it suggests a range for incremental cost using the best case cost (ACT low cost, TKR high cost) and the worst case cost scenarios (ACT high cost, TKR low cost) of £2,400 to £7,600.

For the 10 year model the incremental cost per QALY gained for best case (ACT low cost, 80% good outcome, TKR high cost, 40% good outcome with comparator) was £1,700. And, for worst case (ACT high cost, 60% good outcome, TKR low cost, 90% good outcome comparator) £13,700. This model shows that incremental cost per QALY figure is sensitive to the costs of ACT and the probability of good outcome with ACT.

5.7 Limitations of the economic analysis and other concerns

Many of the limitations of the analysis presented here have been raised earlier and stem from the limitations of the effectiveness evidence. In addition, the decision analysis was limited to considering outcomes over a 10-year time frame (rather than over the patients remaining life time) and focused on an important end-point, namely, total knee replacement. Knee replacement whilst increasingly safe is associated with significant morbidity and a limited life span for the artificial joint. It was assumed that the costs of TKR were incurred at the end of

the 10-year period and that requirement for TKR when comparing the two treatment options might vary substantially. Projecting outcomes further forward in time would require a consideration of the down side of TKR such as the failure rate of TKR and the need for revision of a joint replacement in time.

The social costs of poor knee function for example loss of employment, particularly in those with physically demanding occupations, and the consequent impact of employment on general health and therefore health related quality of life, have been ignored in this report. The impact of patient disability on families, and the state, have also been ignored. The impact of these factors, when comparing the two therapeutic options in this report, do not appear to be substantially different assuming equal clinical outcomes.

Finally, in assessing outcomes of interventions emphasis has been given to an overall outcome, usually reported as a global outcome (often expressed as excellent, good, unchanged or poor) or by stratifying the scores obtained from knee outcome scoring systems into a global outcome. There are difficulties in converting knee scoring systems into a global outcome. For example the proportion of the same patients rated excellent for the Lysholm, Hospital for Special Surgery, and Cincinnati knee scoring systems varies between 23 to 76%⁷⁹. This is due to differences in the content of rating systems and the relative weight given to different domains of an individual rating system. It is hoped that this problem was minimised by using a dichotomous classification of 'good' or 'bad' for outcomes and by exploring an adequate range of outcomes in sensitivity analysis. There are similar concerns about using X-rays as end-points, or surrogates, for determining the extent of cartilage damage within a knee joint in long term follow study especially since the relationship between cartilage loss seen at arthroscopy correlates poorly with the degree of change seen on a radiograph⁸⁰.

Table 10 - Base case 10 year expected costs and QALYs for all pathways

	Base Probability	QALY	<i>QALY discounted</i>	Cost	<i>Cost discounted</i>	Incremental cost per QALY	<i>Incremental cost per QALY (discounted)</i>
ACT/ good outcome/ no further surgery	0.75	5.84	3.92	£7,838	£7,584	-	-
ACT/ poor outcome/ no further surgery	0.09	0.55	0.36	£941	£910	-	-
ACT/ poor outcome/ further surgery/ no TKR	0.12	0.73	0.49	£1,422	£1,363	-	-
ACT/ further surgery/ TKR	0.04	0.21	0.14	£648	£557	-	-
ACT COMBINED	1	7.34	4.92	£10,848	£10,414	-	-
Comparator/ good outcome/ no more surgery	0.70	4.45	2.92	£1,995	£1,758	-	-
Comparator/ poor outcome/ no more surgery	0.06	0.37	0.24	£171	£151	-	-
Comparator/ poor outcome/ further surgery/ no TKR	0.168	1.02	0.69	£714	£631	-	-
Comparator/ further surgery/TKR	0.072	0.38	0.25	£619	£456	-	-
COMPARATOR COMBINED	1	6.21	4.10	£3,499	£2996	-	-
INCREMENTAL (ACT-COMPARATOR)	-	1.13	0.82	£7,349	£7418	£6,544	£9,129

Note: values are reported rounded

Table 11 - Sensitivity Analysis: Incremental expected costs and QALYs.

Scenario	Incremental QALY	<i>Incremental QALY discounted</i>	Incremental cost	<i>Incremental cost discounted</i>	Incremental cost per QALY	<i>Incremental cost per QALY discounted</i>
2 year follow-up			£7,599	£7,599		
high cost ACT, low cost TKR			£2,398	£2,398		
low cost ACT, high cost TKR						
10 year follow-up						
worst case	0.75	0.58	£7,992	£7,906	£10,670	£13,733
best case	1.36	0.95	£1,375	£1,647	£1,011	£1,734
base case except ACT £3800	1.12	0.81	£2,149	£2,218	£1,913	£2,730
base case except ACT £6000	1.12	0.81	£4,349	£4,418	£3,873	£5,437
base case except ACT £7500	1.12	0.81	£5,849	£5,918	£5,208	£7,283
base case except ACT good outcome 0.6 (poor 0.4)	0.85	0.62	£7,588	£7,599	£8,972	£12,189
base case except ACT good outcome 0.8 (poor 0.2)	1.21	0.88	£7,269	£7,357	£4,943	£8,360

6 Summary of results

6.1 Effects

The natural history of cartilage defects within a knee joint is poorly understood. Symptoms may vary from no symptoms at all to symptoms of pain, locking, giving way and swelling of the knee. However long-term follow-up of patients with osteochondritis dissecans, a defect of cartilage and bone, over 10 or more years shows that over a third develop at least moderate osteoarthritis.

ACT is reported in most case series to improve symptoms associated with knee cartilage defects in approximately 70% of cases using a patient-centred global outcome score. This improvement is sustained for a minimum of 2 years.

Other surgical treatments for cartilage defects, or no surgery, also appears to improve symptoms in a similar proportion of patients, for similar periods of time, but less consistently.

For example the range of patients doing well after 2 years lies between 10% and 95%. This presumably reflects differing patient populations as much as the different techniques used. 11.4% to 21% of patients treated with ACT and between 3.5 to 65% of those treated with other surgical procedures require further surgical treatment by arthroscopy within 2 years of primary surgery.

Treatment failure after ACT, 3 years after surgery, occurs in up to 7% of cases.

6.2 Effectiveness

This cannot be determined with certainty since many potential biases could have influenced the analysis reported here. A large number of assumptions have been made in conducting the decision analysis. ACT has the potential for reducing the requirement for total knee replacement in those with large, full thickness cartilage defects in the knee joint although whether whether other, less expensive and less demanding treatments can deliver similar benefits is unclear.

6.3 Cost-utility

A cost-utility analysis was only possible with the 10-year follow-up model. The incremental cost per QALY gained with ACT under the base case assumptions is £9000 (lowest estimate £1,700, highest £13,700). This is determined solely from the viewpoint of the NHS. These figures are subject to the assumptions and uncertainties described in previous sections

7 Implications and conclusions

A major factor that influences the assessment of all therapies of cartilage defects is that most lesions, in contemporary practice, have been identified through arthroscopic examination of knee joints. The natural history of these lesions is ill understood and thus judging outcomes of any surgical intervention is fraught with uncertainty. It is presumed, largely on epidemiological studies of athletes who have sustained knee injuries, and on long term follow up studies of osteochondritis dissecans diagnosed radiographically, that patients, particularly adults, with large full thickness cartilage defects have a high risk of developing osteoarthritis. Most of the studies identified in this report were case series with all the biases inherent in such studies. In addition, there is considerable patient heterogeneity and multiple interventions are often carried out for an injured knee joint, further complicating assessment of a particular treatment. Some of these issues may be addressed by parallel group studies currently underway but it is unlikely that randomised studies over 10 to 20 years will be conducted. Such time scales are required to determine critical outcomes relating to knee function. Therefore, observational studies, of high quality with long follow up times, will be needed to inform judgements on the effectiveness of ACT.

On the basis of the available literature no definite conclusions can be drawn about the effectiveness of ACT which should be regarded as an experimental procedure. However on these grounds almost all other therapeutic options for treating knee cartilage defects, save perhaps arthroscopic debridement, might be regarded as experimental. Since all of the randomised studies involving ACT are still recruiting patients it is unlikely that useful data from these reports will be available for at least a further 2 years. Until that time analysis of case series with longer follow-up times will remain the source of the most useful data. It is recommended that patients believed to be suitable for ACT are included in randomised trials co-ordinated at a National level. Routine commissioning of ACT, on the basis of data reviewed here, cannot be recommended. This decision, however, should be kept under review in the light of any additional information, particularly high quality data that suggests that cartilage defects identified arthroscopically and followed for at least 10 years results in a substantial risk of end-stage osteoarthritis.

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Conflict of interest

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8 Appendices

Appendix 1: Excluded studies (main reason for exclusion)

Appendix 2: Some commonly used clinimetric scoring systems for assessment of knee of disorders

Appendix 3: Year on year utility values for specified pathways

Appendix 4: Unit costs and sources

Appendix 5: Cost estimates for procedures

Appendix 1 - Excluded studies (main reason for exclusion)

Autologous Chondrocyte Transplantation

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surgery. Abstract. International Cartilage Repair Society, Boston, 1998. (No patient outcomes)

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Other Treatments for Cartilage Defects (see methods for inclusion criteria)

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Appendix 2 - Some commonly used clinimetric scoring systems for assessment of knee of disorders

Scale	Description
Lysolm Score ^a 100=best, 0=worst	Scores completed with patient collaboration. Items include limp, requirement for a support (e.g. crutch), stairclimbing, squatting, walking, running and jumping, pain, swelling, and thigh atrophy.
Noyes (Cincinnati) ^b Symptom rating scale (10=best, 0=worst)	Six patient categories e.g. normal knee, able to work and do sport with jumping, hard pivoting is graded 10 points, severe unrelieved symptoms with activities of daily living graded 0 points. A sports rating scale (100 to 0), functional scale assessing daily living activity (120-0), sporting activity (100-0) and aspects of clinical examination such as pivot shift test, degree of crepitus and range of motion may also be incorporated in a detailed scheme for final rating
Knee Society Scoring System ^c 200=best, 0=worst.	The goal of this scoring system is to evaluate outcome of knee arthroplasty. Assesses pain, function i.e. walking, stairs and clinical features such as range of motion, stability, alignment, flexion contracture, and extension lag. The assessment consists of two components first a knee rating system which includes pain (50 points), stability (25) and range of motion (25). Second a functional assessment which considers walking distance (50 points) and stair climbing (50 points) with deductions for use of walking aids.
Hospital for Special Surgery ^d 100=best, 0=worst.	Scores determined from symptom severity and clinical examination. The following features are included: function including walking, transferring, and climbing stairs (22 points), pain (30 points), range of motion (18 points), muscle strength (10 points), deformity (10 points), instability (10 points).
International Knee Documentation Committee ^e	100=best, 0=worst. The following items are rated (according to the scale: normal, nearly normal, abnormal and severely abnormal): patient assessment of function, symptoms, range of motion, and ligament examination.

^a Lysolm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med* 1982;10:150-4.

^b Noyes FR, et al. A rationale for assessing sports activity levels and limitations in knee disorders. *Clin Orthop* 1989;246:238-249.

^c Insall JN, et al. Rationale of the knee society clinical rating system. *Clin Orthop* 1989;248:13-14.

^d Ranawat CS, et al. Duo-condylar knee arthroplasty. *Clin Orthop* 1976;120:76-82.

^e Irrgang JJ, Ho H, Harner CD, Fu FH. Use of international knee documentation committee guidelines to assess outcome following anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc* 1998;6:107-114.

Appendix 3 - Year on year utility values for specified pathways

Yearly utility values for 10 year economic analysis												
Decision analysis pathway	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	Total	Discounted (6%)
Good outcome after ACT	0.6 43	0.7 95	7.79 8	5.233								
Good outcome after comparator treatment	0.6 43	0.7 95	7.79 8	4.177								
Poor outcome post-ACT, no surgery	0.6 43	6.43	4.013									
Poor outcome post-comparator, no surgery	0.6 43	6.43	4.013									
Poor outcome post-ACT, further surgery but not TKR	0.6 43	0.4 43	0.6 43	0.6 43	0.6 15	0.6 15	0.6 15	0.6 15	0.6 15	0.6 15	6.06 2	4.103
Poor outcome post-comparator, further surgery but not TKR	0.6 43	0.4 43	0.6 43	0.6 43	0.6 15	0.6 15	0.6 15	0.6 15	0.6 15	0.6 15	6.06 2	4.103
Poor outcome post-ACT, further surgery, then TKR	0.6 43	0.4 43	0.6 15	0.6 15	0.6 15	0.6 15	0.4 43	0.4 43	0.4 43	0.3 59	5.23 4	3.492
Poor outcome post-comparator, further surgery, then TKR	0.6 43	0.4 43	0.6 15	0.6 15	0.6 15	0.6 15	0.4 43	0.4 43	0.4 43	0.3 59	5.23 4	3.492

Yearly utility values for 2 year economic analysis				
	0-1	≥ 2	Total	Discounted (6%)
Decision analysis pathway				
Good outcome after ACT	0.643	0.795	1.438	<i>1.393</i>
Good outcome after comparator treatment	0.643	0.795	1.438	<i>1.393</i>
Poor outcome post-ACT, no surgery	0.643	0.643	1.286	<i>1.250</i>
Poor outcome post-comparator, no surgery	0.643	0.643	1.286	<i>1.250</i>
Poor outcome post-ACT, further surgery but not TKR	0.643	0.643	1.286	<i>1.250</i>
Poor outcome post-comparator, further surgery but not TKR	0.643	0.643	1.286	<i>1.250</i>
Poor outcome post-ACT, further surgery, then TKR	0.643	0.359	1.002	<i>0.982</i>
Poor outcome post-comparator, further surgery, then TKR	0.643	0.359	1.002	<i>0.982</i>

Appendix 4 - Unit costs and sources

	Orthopaedic consult	Knee MRI	Knee arthroscopy (day case)	Knee arthroscopy (elective)	Primary total knee replacement	ACT	Rehabilitation / physiotherapy
Bryan S, Parry D. Data on file (1999). 11 NHS Trusts	First consult: £90 Follow-up: £50	£140	£510	£800	-	-	Single visit: £50
Royal Orthopaedic Hospital NHS Trust	-	£444*	£482	£1106	£3652**	£8063 (1998), £8466 (1999)†	-
Minas T, Am J Orthop 1998.	-	-	-	-	-	Mean £17160 (range 11,287- 24,615)	-
Lindahl A, et al, unpublished, 1999.	-	-	-	£772	-	£7716 (range £4630-£18,519)	Post ACT £6279; Post- arthroscopy £1042
NHS Reference costs 1998 (www.doh.gov.uk/nhsexec/ref costs/)	-	-	£511	£669 (1998), £702 (1999) †	£4339 (1998), £4556 (1999) †		

^aDollar rates have been converted to sterling using the current exchange rate of £1=\$1.62 (Financial Times July 31, 1999). ^b Follow-up regime for rehabilitation post ACL reconstruction is 2 visits per week for 6-8 weeks followed by one visit per week or per fortnight for up to 4 months. Total visit range 20-32 visits (Sports Physiotherapist, Department of Physiotherapy, University Hospital Birmingham). Rehabilitation following meniscus surgery 12-18 physiotherapy visits. *Radiologist costs included. † Estimated costs for 1999 allowing for 5% inflation. Current charge for Genzyme Tissue Repair chondrocyte service is £6499, for Verigen the cost is £2778. ** Recent US sources indicate an average cost of £6680^a, whilst a British source from 1996 suggest a figure of £4134^b (£4558 for 1999, assuming an incremental cost of 5% p.a.)

^a Iorio R, Healy WL, Richards JA. Comparison of the hospital cost of primary and revision total knee arthroplasty after cost containment. Orthopedics 1999;22:195-9.

^b James M, St Leger S, Rowsell KV. Prioritising elective care: a cost utility analysis of orthopaedics in the north west of England. J Epidemiol Community Health 1996;50:182-9.

Appendix 5 - Cost estimates for procedures over ten years

	Total costs	Discounted ^b (6%)
ACT ACT (£8,000)*, initial rehabilitation (£1,000) ^a , follow up costs (8 outpatient visits over 2 years; £400), 3 visits per annum for 7 years (£1050).	£10,450	£10112
Comparator treatments Initial procedure (£850)**, rehabilitation (assuming they are similar to post-arthroscopy costs; £550), follow-up (as above, first 2 years £400, subsequent 7 years £1050).	£2,850	£2512
ACT, requiring further surgery but not TKR ^c ACT and rehabilitation as above (£9000), further surgery and rehabilitation (arthroscopy, £850, rehabilitation £550), follow-up costs as above	£11,850	£11,358
Comparator treatments, requiring further surgery but not TKR <i>Initial procedure and rehabilitation as above (£1400), further surgery and rehabilitation as above (£1400), follow up costs (£1450)</i>	£4,250	£3758
ACT requiring further surgery and TKR <i>ACT poor outcome, further surgery and follow-up as above except for no final year follow-up as this is included in the TKR HRG cost (£11700), total knee replacement (£4500)</i>	£16,200	£13,933
Comparator treatments requiring further surgery and TKR <i>Comparator treatments poor outcome, further surgery and follow-up as above except for no final year follow-up as this is included in the TKR HRG cost (£4100), total knee replacement (£4500).</i>	£8,600	£6,333
<p>^a Data are available for rehabilitation post-ACT from Lindhal et al, these are judged to be high for the UK and it is assumed that costs post-ACT are similar to costs post-ACL repair i.e. 20-32 physiotherapy visits (£600-960). ^b It is assumed that further surgery following any intervention is required at 2 years and that TKR is required at the end of the 10-year period. ^c A small proportion of patients in the Cartilage Repair Registry had a further transplantation (0.3%). This rate is not included in estimating the costs of further surgery. * Mean of unit cost from Royal Orthopaedic Hospital Birmingham and Lindhal et al. However if minimum costs are assumed i.e. charges reported for Verigen and the cost of 2 day case arthroscopic procedures the base cost of ACT including rehabilitation and follow-up is £6360. **Mean unit cost of in-patient arthroscopy</p>		

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