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Rapid review

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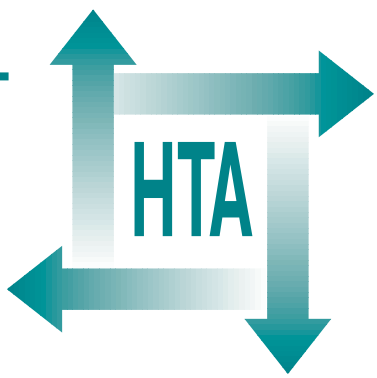

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Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review

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Contents

Glossary and list of abbreviations

ACL	anterior cruciate ligament
ACT	autologous chondrocyte transplantation
Arthroscopy	examination of the internal structure of a joint, by means of a fibre-optic scope. Surgical procedures may be carried out during this investigation
Avascular necrosis	damage to bone and cartilage due to a local loss of blood supply
BIDS	Bath Information and Data Services
Cartilage/ chondral defect (or fracture)	loss of the cartilage lining the end of a bone; these defects are of variable thickness
Cost-minimisation analysis	economic analysis used when outcomes are equivalent, irrespective of the intervention used. The aim is to determine the most efficient way of achieving a given goal
CPM	continuous passive motion
DARE	Database of Abstracts of Reviews of Effectiveness
DES	Development and Evaluation Service
DGKKT	deutsche Gesellschaft für Knorpel- und Knochenzell-transplantationen*
DVT	deep venous thrombosis*
FC	femoral condyle*
FCE	finished consultant episode*
FDA	Food and Drug Administration (USA)
HCHS	Hospital and Community Health Service*
HSS	Hospital for Special Surgery*
Hyaline cartilage	cartilage that is usually found at the ends of bones, within a synovial joint
ICRS	International Cartilage Repair Society*
LFC	lateral femoral condyle*
MACI	matrix-induced autologous chondrocyte implantation
MeSH	Medical Subject Headings
MFC	medial femoral condyle*
MRI	magnetic resonance imaging
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Clinical Excellence
OA	osteoarthritis. A disease of joints in which there is evidence of cartilage loss and an accompanying reaction in bone
OCD	osteochondritis dissecans. Detachment of fragment(s) of cartilage, with or without bone, into a joint; arising either spontaneously or as a result of injury
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
QALY	quality-adjusted life-year

* Used only in appendices or tables

continued

continued

QoL	quality of life*
RCT	randomised controlled trial
RJAH	Robert Jones and Agnes Hunt (Orthopaedic and District Hospital NHS Trust)
ROH	Royal Orthopaedic Hospital (Birmingham)*
SD	standard deviation*
SEK	Swedish krona
SF-36	Short Form with 36 Items
TKR	total knee replacement*
WOMAC	Western Ontario and McMaster Universities osteoarthritis index*

* Used only in appendices or tables

Executive summary

Background

Proposed service

Autologous chondrocyte transplantation (ACT) is a novel surgical approach used to treat full-thickness cartilage defects in knee joints. Small grafts of normal cartilage removed from the patient's diseased joint are treated in a laboratory to obtain cartilage cells. These cells are cultured to expand the cell population and reimplanted a few weeks later into areas where cartilage is denuded by disease. The aim of this procedure is to restore normal cartilage to the ends of bones and thereby restore normal joint function.

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 individuals sustaining a haemarthrosis following a knee injury may have cartilage damage.

Objectives

This systematic review of the available evidence was performed to:

- describe the types of knee disease for which ACT has been applied, the natural history and epidemiology of these conditions, and alternative treatment options
- determine long-term clinical outcomes following ACT and other surgical procedures for knee cartilage defects
- examine the economic evidence and consider the economic gains resulting from ACT.

Methods

To analyse the effectiveness of treatment and the resultant economic impact, a systematic review of the literature, involving a range of databases, was performed. In addition, contact was made with leading researchers and industry. Full details are described in the main report.

Results

Number and quality of studies and direction of evidence

Of 46 identified reports, 17 met the criteria for inclusion in this review. Eight of the included reports were available as abstracts only. At least 2600 patients appear to have been treated with ACT. All included reports were case series with a variable length of follow-up. With one exception, all the studies reported improvement in patient status, usually over a follow-up period of less than 2 years.

Summary of benefits

The outcome of ACT surgery was rated as 'good' or 'excellent' by approximately 70% of patients 2 years after treatment. Approximately 16% of patients required further arthroscopic surgical procedures during follow-up, and treatment was judged to have failed in 3–7% of patients. For comparator treatments, the outcome was rated as 'good' or 'excellent' in 10–95% of patients 2 years after treatment.

Economic review

The reports of two studies, one based in the USA and the other in Sweden, included economic data. Neither study compared ACT with other treatments. Using data from these studies and other sources, it was estimated that ACT performed in the UK would cost £4667 or £8167 for cell culture and surgery, depending on which service provider was used for cell culture. Incremental cost over 2 years, when set against comparator treatments, was estimated to be £3771 or £7271 (base case) for cell culture, surgery and rehabilitation. Using the OsCell facility for cell culture (Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust), this figure would be £3167.

Conclusions

The reported literature on ACT and comparators 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. The cost-effectiveness analysis is similarly limited by the poverty of the effectiveness data on both

ACT and comparators, the lack of long-term follow-up and the lack of empirical data for some of the parameters in the model used.

Recommendations for research

Further studies are required to:

- provide more accurate data on the occurrence of hyaline cartilage defects, including defects that arise acutely and those that are secondary to other types of knee injuries
- clarify the relationship of cartilage defects to clinical symptoms
- evaluate in detail the natural history of cartilage defects diagnosed by modern arthroscopic methods
- compare ACT with other treatments deemed appropriate, based on randomised trials currently in progress or planned
- examine, in prospective randomised trials, issues such as differences in outcome in patient subgroups (e.g. the suggested poor outcomes in patients with patellar defects), with patients followed for as long as possible
- address the deficiencies in evaluating the clinical outcomes of knee injury and incorporate measures of general health status
- consider study designs, other than randomised trials, that might be used to assess complex interventions such as those required in complex knee injuries.

Chapter 1

Aim and background

Aim of the review

The objectives of this review are to:

- describe the types of knee disease for which autologous chondrocyte transplantation (ACT) has been applied
- describe the natural history and epidemiology of these conditions
- describe alternative treatment options
- determine long-term clinical outcomes following ACT and other surgical procedures for knee cartilage defects
- review the economic evidence and consider the economic gains resulting from ACT.

Background

Description of underlying health problem

It is believed that injuries to knee hyaline cartilage predispose individuals to osteoarthritis (OA) in later life and eventually to a requirement for knee replacement surgery because of increasing pain and disability. This view is based on experimental observations that show hyaline cartilage has a limited capacity for repair[1,2] and on epidemiological studies that show a relationship between knee injury and later development of OA.[3] Normal hyaline cartilage provides a smooth surface at the ends of bones, allowing virtually frictionless movement within a joint. Knee injuries, often as a result of sporting activity, may lead to damage of the bone, hyaline cartilage, meniscus (also called 'cartilage' by lay persons) and ligament (*Figure 1*). These knee injuries commonly occur in combination and potentially require a range of surgical approaches. The loss of cartilage alone is referred to as a 'chondral fracture', while the loss of bone and cartilage is known as an 'osteochondral fracture'. Osteochondral fractures occur more commonly in adolescents because it appears that, in this age group, the plane of weakness at a joint lies in bone rather than at the junction of cartilage and bone.[4,5]

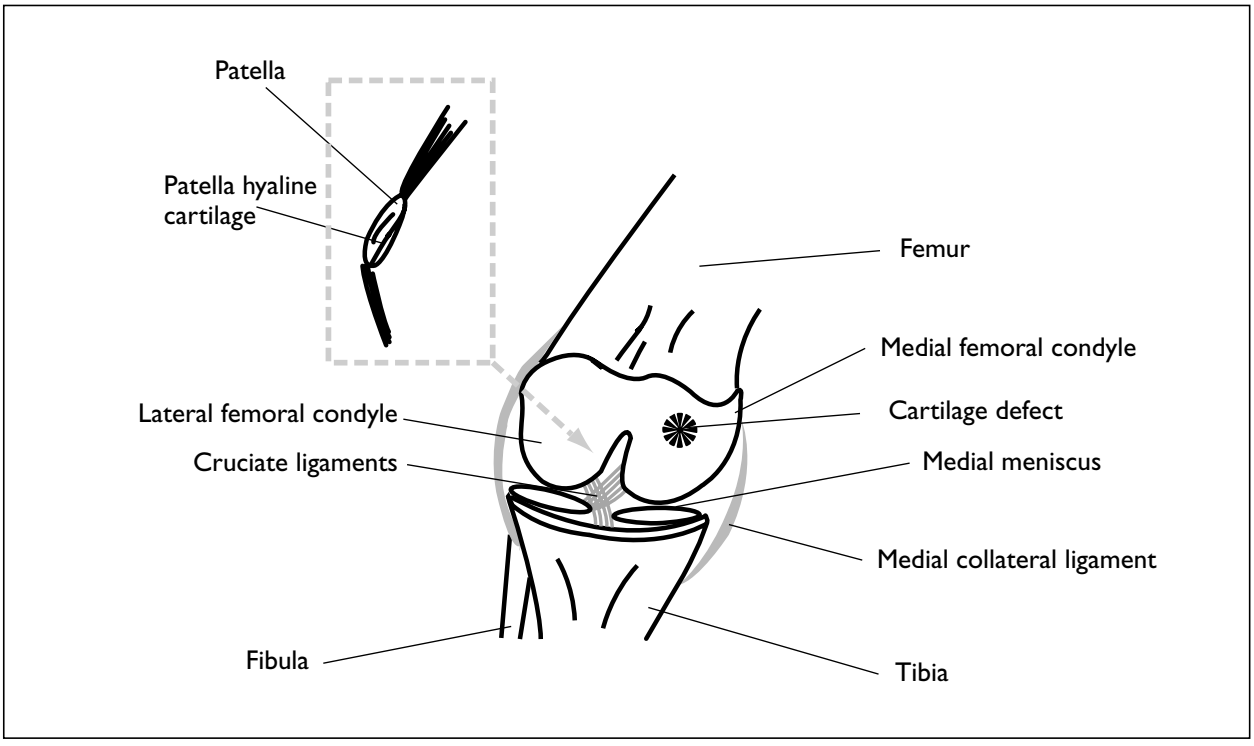

FIGURE 1 *Diagram of the knee joint (anterior aspect) and patella (viewed from the side, as a boxed inset)*

Aetiology, diagnosis and natural history

Cartilage damage can be caused directly from injury, by various types of arthritis or spontaneously in a condition called osteochondritis dissecans (OCD). Cartilage damage may also arise because of knee instability or abnormal loading, for example, secondary to a ligament injury[6] or diseased menisci.[7] Spontaneous loss of a fragment of bone and cartilage from a joint occurs in OCD. However, this term is not always applied consistently and may be used to describe bone and cartilage loss due to injury. In young persons, the most common cause of hyaline cartilage damage is sporting injuries. The natural history of hyaline cartilage lesions or chondral fractures that follow injury in humans is not known. Cartilage lacks a nerve supply, and isolated cartilage damage does not directly cause pain. Therefore, a proportion of patients with significant hyaline cartilage damage do not experience pain and may not experience any other symptoms associated with knee injury. Those patients who do experience symptoms with the loss of hyaline cartilage of full thickness have symptoms similar to those of a meniscal tear.[8] Patients complain of knee pain, knee swelling, joint locking (i.e. the joint becomes stuck in one position) and giving way of the joint. Knee injuries of various sorts may cause a chondral or osteochondral defect. Possible causes of these injuries include a direct shearing force on the medial or lateral femoral condyle due to a heavy fall on a bent knee, a direct impact such as a kick on a bent knee or patellar dislocation. Rotary forces on the knee while weight-bearing, for example, a sudden or unintended change in direction in a skier or footballer, may also produce similar injuries.[3,9]

Cartilage defects are usually diagnosed by arthroscopy,[10] although they may be seen on magnetic resonance imaging (MRI). Osteochondral fractures, however, because they involve bone, may be seen on X-rays. OCD resembles osteochondral fracture in that a segment of joint cartilage and some bone becomes detached from the joint surface. Characteristically, OCD is a concentric lesion that involves the medial femoral condyle in a knee. It develops spontaneously, without a precipitating injury, often during the second decade of life.[11] Some experts believe that OCD arises as a result of localised avascular necrosis of the subchondral bone, causing separation of a fragment of bone and cartilage.[12] Long-term studies of OCD provide the only source of information on the likely natural history of cartilage defects in the knee joint. For example, Linden[13] found that, in patients with OCD, 55% of adults, but no children, went on to develop severe OA. In this study, 58 patients were followed for an average of 33 years. Linden suggested that tissue repair was more effective in children and that OA associated with OCD occurred some ten years earlier in life than other forms of OA. However, many adults with OCD are symptom-free for up to 20 years before they develop evidence of OA.

Laboratory studies

Defects in hyaline cartilage may repair by two main mechanisms: (1) intrinsic repair, by which tissue regenerates from cartilage alone, and (2) extrinsic repair, by which other cell types, for example, synovial or bone marrow cells, contribute to repair (reviewed by Stockwell[14]). It is widely accepted that only the latter mechanism is effective. Intrinsic repair mechanisms appear to be ineffective due to the limited capacity of cells in hyaline cartilage (chondrocytes) to respond to large defects arising from injury or surgery. Thus, partial-thickness cartilage defects in joints rarely heal because bone marrow precursor cells cannot contribute to repair. Cells with a capacity to repair cartilage may come from bone marrow, synovial tissues[2] (or perhaps synovial fluid) and the periosteal lining of bone. Healing often occurs by the formation of fibrocartilage, a tissue that is softer and less durable than hyaline cartilage.[15]

Animal experiments, in which cartilage has been damaged in order to learn about treatment, show that various methods, including chondrocyte transplantation, are inconsistent at producing repair. In general, results in rabbits appear to be more favourable than results in other species, especially dogs.[1,16] In addition, postoperative use of continuous passive motion (CPM) seems to improve cartilage healing (see *Treatment options* below), suggesting that certain types of physical stimulation can improve cartilage healing.[17] Experimental wounding of cartilage, in animal models, causes chondrocyte death in the vicinity of the wound, which may affect the ability of any new tissues formed in the wound to bond with existing cartilage. Inadequate bonding between newly formed tissue and existing tissue is likely to compromise tissue integrity.[18] Therefore, with time, because of a failure of repair tissues to integrate with existing tissues, joint disease may follow regardless of whether hyaline or fibrocartilage is formed during repair.

Prevalence and incidence

The prevalence or incidence of hyaline cartilage damage in knee joints is not known, partly because

cartilage defects may arise from a variety of direct injuries. These defects may arise indirectly from another knee injury, many months or years after the primary insult. In addition, patients with knee symptoms due to cartilage defects may present to a variety of medical practitioners and may be evaluated with differing diagnostic approaches. Patients with serious knee symptoms may be investigated by an arthroscopic examination of the knee joint. Data from a large database of arthroscopies show that full-thickness loss of cartilage, in patients under the age of 40 years, accounts for 5% of all procedures.[19] Unfortunately, prevalence and incidence cannot be estimated from this study because precise patient numbers were not reported. In acute knee injuries involving haemarthrosis (bleeding into the joint), about 20% of knees show cartilage surface defects (chondral fractures), often with other damage within the knee, such as lesions of the anterior cruciate ligament (ACL) and menisci.[20] In comparison with injury-related cartilage damage, the incidence of OCD is low (30–70 patients per 500,000 population), and this condition occurs primarily in patients between the ages of 10 and 30 years.[21]

Some reports suggest that isolated cartilage damage is relatively uncommon, occurring in only eight patients in a series of over 1000 arthroscopies.[22] However, significant cartilage injury, as judged by microscopic appearances of cartilage over areas of 'bone bruising' or bony contusion seen on MRI, appears to be fairly common.[23] 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 of cartilage loss in about 50% of cases, upon follow-up MRI.[24] These data suggest that cartilage damage may frequently go unrecognised, especially as conventional MRI scans are relatively insensitive for detecting cartilage defects, compared with arthroscopy.[25]

Impact on quality of life

Knee injuries requiring hospital attention are associated with a significant impact on quality of life. For example, scores on the Short Form with 36 Items (SF-36) health questionnaire indicate that physical functioning, role limitations due to physical problems, pain and social functioning are all significantly worse in this patient group, compared with scores for the general population.[26] For patients with advanced knee disease requiring joint replacement surgery, the impact on quality of life, rated by the EuroQoL index, is as low as 0.359 (with 1.00 representing perfect health).[27] In professional sportsmen and sportswomen and in individuals who have physically demanding jobs, cartilage injuries may lead to loss of employment, in addition to limiting quality of life.

Current service provision

Treatment options

There is no uniform approach to managing hyaline cartilage defects in knees.[28–39] The majority of defects are identified during arthroscopic surgery. Therefore, patients will at least have a knee washout because this procedure is an element of arthroscopy. In addition, surgeons will frequently trim loose tissue flaps (debridement) in the belief that such tissues might be contributing to patient symptoms. Other surgical procedures used to treat cartilage defects include 'marrow stimulation techniques', various tissue grafts taken from outside the joint (e.g. rib or periosteum grafts) and grafts of normal cartilage cores from within an affected joint (mosaicplasty). A brief description of key techniques is given in *Table 1*.[29–39] In addition to surgical interventions, the postoperative management of patients varies considerably. For example, there are various regimens for weight-bearing and physiotherapy techniques, including the postoperative use of CPM. In CPM, the affected knee is subjected to continuous involuntary movements, by a mechanical device, to provide stimulation in order to improve range of motion. This technique also provides a mechanical stimulus to knee structures in order to promote healing. It is unknown whether cartilage healing is promoted by CPM in humans. This report is not concerned with non-operative management and medical therapies. We focus on surgical management but acknowledge that variations in postoperative rehabilitation may influence the outcomes of any surgical approach.

Most reports of the treatment of knee hyaline cartilage defects describe a series of cases without historical or concurrent controls. Many studies describe patients with established knee OA who show changes on X-rays, rather than patients with localised cartilage loss following knee injury. Such patients with OA are believed to be unsuitable for ACT, as discussed in *ACT: indication, diffusion and potential costs*. Not surprisingly, in view of the uncertainties regarding the management of cartilage defects, surveys of surgeons show considerable variation in diagnostic and surgical approaches. A survey describing responses from

TABLE 1 *Treatment options for cartilage defects in knee joints*

Method	Description and purpose
Knee washout	To remove intra-articular debris and potentially harmful enzymes, and to reduce inflammatory reactions.[29] Arthroscopic or percutaneous approaches are used
Arthroscopic debridement	Usually refers to the removal of loose cartilage tissue surrounding a cartilage defect, accompanied by a knee washout[30]
Marrow stimulation techniques	Include 'abrasion arthroplasty', subchondral drilling, microfracture and 'spongialization'. Used for full-thickness or nearly full-thickness cartilage defects. The defect's edges are debrided, and the base of a defect (subchondral bone) is breached in various ways to allow access for the entry of bone marrow cells, which can potentially stimulate healing. A motor burr (abrasion arthroplasty[31]), drill, surgical pick or, more radically, subchondral bone resection (spongialization[32]) can be used to breach the base
Mesenchymal cell grafts	Periosteum (a delicate cell layer adjacent to and overlying bone) and perichondrium (a cell layer around ribs) are capable of producing hyaline cartilage. Grafts of these tissues have been used to treat knee cartilage defects[33,34]
Woven carbon fibre grafts	Man-made fibre discs (e.g. made of carbon, silicon or collagen) may be used to fill in cartilage surface defects[35]
Mosaicplasty	Cylinders of normal cartilage and bone (approximately 4.5 mm in diameter), from 'non-weight-bearing' areas of an affected knee, are removed and placed into cartilage defects during a single surgical procedure. These 'autografts' result in the formation of a patchwork or mosaic.[36] Usually restricted to defects < 2 cm^2 in diameter. Contraindicated in established OA[37]
Osteochondral grafts	Grafts of mature cartilage with a supporting layer of bone (2–10 mm thick), fresh or frozen, are obtained from a donor (allografts). Usually used for compound injuries in which restoration of bone is a priority[38]
Paste grafts	A newly described technique in which cartilage and bone harvested from a non-weight-bearing area of an affected knee (as for mosaicplasty) are formed into a paste and packed into a cartilage defect[39]
ACT	Autografts of cartilage, from non-weight-bearing areas of an affected knee, are removed during arthroscopy. Grafts of 200–300 mg (an area of approximately 0.5 x 1.0 cm) are treated in a laboratory to extract chondrocytes, which are cultured for 3–5 weeks to expand the cell population. The cultured cells are later used in a planned second operation. Cells may be frozen in the interim. During the second operation, a cell suspension is injected into a debrided cartilage defect, beneath a specially created lid of periosteum or artificial collagen. Then the defect is sealed with fibrin

255 German surgeons indicates that most surgeons favour marrow stimulation techniques as the primary approach to managing cartilage defects, while other treatments appear to be rarely used.[28] There is no current NHS provision for ACT. However, it appears that at least tens of procedures have been carried out in the UK, although the precise numbers are unknown. Currently, the costs of managing cartilage defects in knees are linked to the costs of managing knee injuries in general and to those of arthroscopic knee surgery in particular.

Requirements for ACT

In order to use ACT to treat patients, an orthopaedic surgeon needs skills in the assessment and treatment of knee injuries, including arthroscopic surgery. In addition, special training is required in the techniques of ACT. Two commercial organisations, Genzyme Corporation (Cambridge, MA, USA) and Verigen Transplantation Service International (Leverkusen, Germany), provide services for chondrocyte culture in the UK. Both these companies also provide training for orthopaedic surgeons with an interest in this area. In addition, Co.don® AG (Teltow, Germany), a biotechnology company, provides this service for the German market, and an in-house facility is in use at the Robert Jones and Agnes Hunt (RJAH) Orthopaedic and District Hospital NHS Trust in Oswestry. All organisations providing commercial services need to prepare cells to an appropriate standard, which is considered in more detail below (see *Quality assurance*).

Description of new intervention

ACT: indication, diffusion and potential costs

Precise criteria for using ACT have not been established. Ideally, patients should have a symptomatic cartilage defect (surface area, 2–10 cm^2) that might include fissuring,

fragmentation or loss of surface cartilage, but not necessarily full-thickness loss of cartilage (Outerbridge[40] grade III or more; see appendix 1). Patients should be aged 15–55 years, and radiographic evidence of OA should be absent. Therefore, the knee joint space should be near normal, and new bone formation (osteophytes, which are a feature of OA) should not be seen.[41] A variety of other relative or absolute contraindications have been suggested, including disease in the patella and multiple small cartilage lesions. Also, patients ideally should have undergone other more conventional surgical approaches or medical treatments before ACT. In practice, however, patients with defects of the patella or multiple defects have had ACT, and many patients treated with ACT have not undergone any other surgical procedure prior to ACT.[42]

The US Food and Drug Administration (FDA) granted a 'biologics' licence to Genzyme Tissue Repair in August 1997 for the commercial use of ACT. The FDA had stipulated a requirement for postmarketing studies to confirm data and also to assess long-term clinical outcomes. In a press release, Genzyme Corporation indicated that two multicentre randomised studies involving more than 300 patients were planned.[43] It was proposed to compare ACT with marrow stimulation techniques or periosteal grafting. Both studies were expected to report in 2003. Some health insurance companies in the USA reimburse the surgical expenses connected with ACT. However, despite a degree of consensus on the appropriate uses of ACT, there is evidence ACT is being used to treat conditions for which it is not indicated.[44]

In the UK, a number of ACT procedures have been carried out by a small number of interested surgeons. To our knowledge, there is no central register of UK surgeons skilled in this procedure, and the total number of procedures carried out in the UK is also unknown. Worldwide, 583 surgeons contribute patient information to a database maintained by Genzyme Tissue Repair. Genzyme promotes chondrocyte transplantation through its tissue repair section Carticel®. The majority of surgeons using Carticel services are based in the USA, Germany and England (12 surgeons as of December 1998). The organisations providing a service for chondrocyte transplantation require skills in the laboratory culture of cartilage cells to an appropriate standard. Currently, Verigen Transplantation Service International also offers this service, through a facility in Copenhagen, Denmark. The biotechnology firm Co.don provides this service for the German market.[45]

In addition, in-house methods for the culture of chondrocytes, for use in human transplants, have been developed and are in use at the RJAH Orthopaedic and District Hospital NHS Trust in Oswestry.[46] A Swedish team (Lindahl A and Peterson L, Göteborg, Sweden) also has in-house expertise and is the largest single group with experience in ACT.[41]

Surgical procedure, postoperative care and follow-up

ACT surgery is briefly described in *Table 1*. Minas and Peterson have provided a more detailed description.[47] Upon initial arthroscopy, in preparation for ACT, the clinician carefully assesses cartilage damage, including the quality of surrounding cartilage, as well as other intra-articular structures and joint stability. Healthy cartilage surrounding the cartilage defect is needed so that a periosteal flap can be sutured over the defect to form a lid. Cartilage biopsies are taken to provide cells for culture. Biopsies provide approximately $2–3 \times 10^5$ cells, which yield 12×10^6 cells after culture. Cartilage biopsies are taken from areas of the knee joint that are not thought to be subject to weight-bearing load. Additional surgical treatment for concomitant injuries (e.g. to ligaments or menisci) or other knee problems (e.g. abnormal tracking of the kneecap) may also be required. Such treatments may be performed at the time of ACT or during other additional operations.

After cell culture, the surgeon begins chondrocyte implantation by opening the knee joint and debriding the cartilage defect thoroughly to expose healthy cartilage. It is believed that contaminating cells from bone marrow increase the risk of fibrocartilage formation. Therefore, care is taken to achieve a contained defect and to avoid penetrating the subchondral plate so that bone marrow cells are not able to enter the defect. If bleeding occurs from the base of the defect, it is controlled by the application of noradrenaline solution. Next, periosteum tissue is procured from the proximal end of the tibia. This delicate tissue is used to form a lid over the cartilage defect. It is secured over the cartilage defect by suturing through normal cartilage or adjacent tissues (such as synovium) surrounding the defect. A watertight drum is created, using a fibrin sealant if necessary. Fibrin is made from a unit of the patient's blood collected preoperatively. Cultured chondrocytes, prepared as a cell suspension, are then injected under the periosteal patch.

Verigen Transplantation Service International has introduced two modifications to this technique.

First, instead of using periosteum to cover the cartilage defect, their method uses a highly purified porcine collagen membrane made of collagen types I and III. This modified technique has the advantage of not requiring a second incision to procure periosteum when cells are implanted. A second modification is the use of cells cultured within a biological matrix. In this technique, called MACI® (matrix-induced autologous chondrocyte implantation; Verigen Transplantation Service International, Germany), cultured chondrocytes are seeded onto an artificially synthesised biological membrane of collagen (I/III), which is then used for implantation. The advantages are that this piece of tissue, which houses cultured and viable chondrocytes, can be cut to size and glued into the cartilage defect.

Cartilage requires many months to heal. Therefore, the results of any attempt at repair should be assessed after many months, preferably many years, especially if the goal of therapy is to avert the risk of joint failure. Minas and Peterson[47] describe three key stages of cartilage repair: cellular proliferation (up to 6 weeks), transition (7–26 weeks) and remodelling (beyond 27 weeks). Because newly formed reparative tissue is vulnerable to mechanical damage in the early postoperative period, rehabilitation is prolonged. Patients are treated with CPM within 24 hours of surgery, for 6–8 hours per day, for the first 6 weeks after surgery. Crutches are used for the first 6 weeks. Thereafter, weight-bearing is permitted to gradually achieve full body weight at 12 weeks. Running is not permitted until after 9 months, and most patients use crutches or a walking cane for 4–5 months.

Quality assurance

The use of autologous tissue to repair cartilage avoids the potential for graft rejection that may arise with foreign tissues. It also reduces the hazards of viral transmission. However, laboratory culture of cells for later injection into patients creates other potential hazards. For example, there is a potential for infecting tissues in the laboratory, in addition to the possibility of failure to cultivate cells adequately, cell death in the laboratory (e.g. when freezing and thawing cells) and errors in labelling samples during acquisition, storage or implantation of tissues. Adequate standards for quality assurance are essential to minimise such hazards. Quality assurance schemes do not appear to be in place in Europe, but a draft European document on the use of somatic cells for therapeutic use is at the stage of public consultation. Genzyme promotes ACT through its tissue repair section Carticel. They are the largest providers of this service worldwide. Genzyme adheres to a quality assurance programme stipulated by the FDA. Based on a series of 304 orders of chondrocyte culture for ACT, only one order (0.33%) was not fulfilled during 1996, but errors in processing "that did not impact on patient safety" were identified in 5% of cell processing activities.[48]

Chapter 2

Effectiveness

Methods for reviewing effectiveness of ACT

Search strategy

Papers were identified using the following search strategies.

1. Electronic databases searches included MEDLINE (Ovid, 1966 to May 2000), EMBASE (Ovid, 1988 to May 2000), the Science Citation Index (Bath Information and Data Services [BIDS] ISI and BIDS Pascal from 1981 to May 2000) and The Cochrane Library (Spring, Issue 1, 2000). The Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Research Register, the NHS Economic Evaluations Database (NHS EED) and the HTA database were also searched (URL: <http://www.york.ac.uk/inst/crd/welcome.htm> accessed 19 March 2000). Medical Subject Headings (MeSH) subject headings and keywords that encompass cartilage diseases, chondrocytes, knee diseases, knee injury, costs, quality of life and autologous transplantation were sought. Details of the search strategy used for MEDLINE and EMBASE, including yields, are shown in appendix 2.
2. Abstracts from meetings of the Cartilage Repair Society (1998–1999) and the American Academy of Orthopaedic Surgeons (1997–1999) were searched.
3. Contact was made with leading researchers.
4. Internet searches were performed using a metasearch engine (MetaCrawler) and the search term 'chondrocyte transplantation' (URL: <http://www.voicenet.com/~bertland/searchf/metasearch.html> accessed 19 March 2000). Of the best-matched hits, 150 were scanned and appropriate links made. The websites of Carticel (URL: <http://www.genzyme.com/prodserv/tissue_repair/carticel/welcome.htm> accessed 19 April 2000), the American Academy of Orthopaedic Surgeons (URL: <http://www.aaos.org> accessed 19 March 2000) and the Cartilage Repair Society (URL: <http://www.cartilage.org> accessed 19 March 2000) were also searched.
5. Also included were any independent studies in the public domain that we had not identified but that were reported in industry submissions to the National Institute for Clinical Excellence (NICE).

We also sought data on other therapies used to treat knee cartilage defects. This search was necessary in order to put ACT into context for our economic analyses. An exhaustive search for comparator treatments, however, was not conducted. This limitation was applied for pragmatic reasons but also because multiple therapies have been used to treat cartilage defects. Therefore, an appropriate and comprehensive search strategy was believed to be outside the remit of this report. We undertook a scoping search on comparator treatments and confined ourselves to English language publications. Studies focusing exclusively on patella cartilage defects were excluded because this defect is considered a relative contraindication for ACT. Data were found by inspecting citation lists of reviews of ACT, by scanning relevant titles and abstracts during ACT searches, and during background and exploratory searches.

All searches were performed up to 6 May 2000.

Inclusion and exclusion criteria

Any report, published or unpublished, in any patient group, that described the use of ACT was included, provided that patient outcome data were available. Studies not reporting patient outcomes, such as those reporting histology or radiology alone, were excluded. If data from the same source were available in multiple publications, the most recent or most complete report was used in order to maximise patient numbers and length of follow-up. Abstracts were included, provided that relevant data were shown. Abstracts reporting data that had been either superseded or described in full reports were not listed in the results or appendices.

Data extraction

Two reviewers abstracted patient outcome data using a specifically designed form. This data extraction form was piloted extensively before use. 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. Two reviewers also extracted data from a selection of important comparator studies.

It was apparent that the nature of knee injury and requirement for concomitant procedures varied in different series. Therefore, data for many variables that indicate patient heterogeneity and that might influence patient outcomes were also abstracted. For example, data on lesion site, size and aetiology, patient age, length of follow-up, concomitant injuries, and the nature and extent of previous intervention were all extracted, if available. Data on global outcomes were given special emphasis and, when possible, were expressed as a dichotomous variable, that is, good or bad (if necessary, by inference) in order to allow comparison between studies.

Length of follow-up, which is an important factor in assessing outcome, was recorded as the minimum length of follow-up, not the mean length of follow-up (unless the former was not available). Data from 'second-look' arthroscopy (i.e. the examination of some treated patients at a follow-up arthroscopy) were included with the aim of identifying whether macroscopic appearance was regarded as acceptable or not. The histology of cartilage biopsies was available for only small numbers of patients. Although such data are of biological importance, there is uncertainty about the relationship of histological appearances to clinical outcome.[49] For these reasons, histological descriptions of transplanted tissue were not extracted.

Quality assessment

All studies of ACT consisted of descriptive case series or cohorts of patients without historical or concurrent controls. Study quality was classified as follows:

A. study reporting clinical outcomes that included patient input (e.g. completing forms) before and after surgery, and a report of adverse effects
B. study reporting clinical outcomes that included patient input before and after surgery, but did not provide an explicit description of adverse events
C. study reporting patient input only after surgery, but no preoperative input
D. study reporting input from clinician or radiographic evaluation only, without any patient input.

Results

Quantity and quality of research

Very few studies with clinical data for patients treated with ACT were found. In total, 46 relevant reports were identified. Of these, 17 reports met inclusion criteria.[42,45,46,50–64] For completeness, a key study by Peterson and colleagues[61,62] is listed twice in the results tables in order to highlight more recent data available in abstract form only. Eight other studies were available as abstracts only. At least 2600 patients appear to have been treated with ACT. Of the 29 excluded reports, 20 were review articles, editorials or news features, six reports included duplicate data or the reports were superseded by data from more recent sources, and three contained no relevant patient data. All the ACT studies are listed in appendix 3, together with the reasons for exclusion, if applicable.

All included studies were case series without historical or concurrent controls. It is uncertain, in most cases, whether authors were describing consecutive cases. Allowing for the problems of such case series, three studies were graded A on our quality assessment scale (see *Quality assessment* above). Included studies described patients with a variety of characteristics. For example, the site(s) and size of lesion, the need for concomitant procedures and the proportions of patients who had undergone prior surgeries varied widely. Aspects of patient heterogeneity and quality classification are shown in *Table 2*.[42,45,46,50–67]

To date, relatively few patients have been followed for an adequate period of time (> 2 years). Ten randomised controlled trials (RCTs), proposed or currently underway, comparing ACT with other interventions were also identified (*Table 3*).

Also identified were two reports considered to be key, based on the number of patients treated and followed for at least 2 years: Peterson and colleagues[61] and the Cartilage Repair Registry maintained by Genzyme Tissue Repair.[42] The results from these two reports are described in detail below in *Assessment of effectiveness*. Clinical outcomes, including adverse effects, of all included studies are shown in *Table 4*. Selected studies of comparator interventions are described below in *Other surgical treatments*.

Assessment of effectiveness

Summary of effectiveness data

Patient characteristics are very variable in studies reporting treatments for cartilage defects (e.g. the

TABLE 2 *ACT included studies: aspects of patient heterogeneity and quality*

Study	Quality	*n*	Patient characteristics				
			Mean age (years)	Defect size (cm^2)	Defect characteristics	Concomitant procedures	Previous surgeries
Bahuaud *et al.*, 1998[50]	C/D	24	27	6	All of full thickness 8 of 24 defects (33%) OCD, 13 of 24 (54%) associated with ligament lesions	NS	NS
Burkhart *et al.*, 1998[51]	B	7	33	4–8	All of full thickness	NS	NS
Cartilage Repair Registry, 1999[42]	A	485	35	4.6	76% of full thickness MFC involved in 61%, LFC in 18%, patella in 7%, trochlea in 13%, tibia in 1%	In 77% of patients (e.g. meniscus surgery in 16%, ligament reconstruction in 6%, fragment reattachment or removal in 14%)	Debridement and lavage in 49%, marrow stimulation in 28%, meniscectomy in 23%, 'primary cartilage treatment' in 59%
Erggelet *et al.*, 1998[52]	B	10	28	5.7	NS	NS	NS
Georgoulis *et al.*, 1998[53]	D	12	28	4.5	MFC involved in 67%, LFC in 33%, inter-condylar notch in 1%	NS	NS
Gillogly *et al.*, 1998[54]	B	25	36	5.7	MFC involved in 51%, LFC in 23%, trochlea in 13%, patella in 11%, OCD in 15%	In 19 of 41 patients (46%) (e.g. ACL repair in 17%, transposition of tibial tubercle in 29%, osteotomy in 2%, meniscus surgery in 2%)	'Surgery directed at chondral injury' in 29 of 41 patients (71%)
Hart & Paddle-Ledinek, 1998[55]	D	16	< 45	NS	Femoral condyles involved in 52%, trochlea in 17%, patella in 40%, tibial condyles in 7%	'Biomechanical procedures' in 64% of patients	NS
Knutsen *et al.*, 1998[56]	B	12	37	NS	NS	NS	NS
Koh *et al.*, 1998[57]	B	26	NS	3.9	MFC involved in 54%, LFC in 12%, trochlea in 31%, patella in 4%	NS	Various surgeries in > 50% of patients
Löhnert *et al.*, 1999[45]	A	20	35	4	MFC involved in 53%, LFC in 19%, patello-femoral joint in 7%, OCD in 20%	NS	NS
McKeon *et al.*, 1998[58]	D	23	38	3.8	All of full thickness MFC involved in 47%, LFC in 19%, trochlea in 22%, patella in 9%, tibia in 3%	In 4 of 23 patients (17%) (e.g. tibial osteotomy in 4%, ligament repair in 4%, hardware removal in 9%)	Mean of 2.4 previous procedures per patient (no details provided)
Minas, 1998[59,60]	B	44	36	5.5	MFC involved in 44%, LFC in 13%, patella in 17%, tibial plateau in 6% Early OA described in 14 of 44 patients (32%) (i.e. osteophytes or < 50% joint space narrowing)	NS	87% of patients had previous knee surgery (mean of 2.5 procedures per patient), 55% had previous marrow stimulation or perichondrial graft

continued

TABLE 2 contd *ACT included studies: aspects of patient heterogeneity and quality*

Study	Quality	*n*	Patient characteristics				
			Mean age (years)	Defect size (cm^2)	Defect characteristics	Concomitant procedures	Previous surgeries
Peterson *et al.*, 2000[61]	A	101	30	4.3	All of full thickness Femoral condyles involved in 44%, patella in 20%, OCD in 19%, multiple lesions in 17%	ACL repair in 18 of 101 patients (18%) Other details NS	49 of 59 patients (83%) had previous procedures, including marrow stimulation, debridement and lavage
Peterson *et al.*, 2000[62]	B	213	NS	4	Femoral condyles involved in 39%, trochlea in 6%, patella in 15%, OCD in 15%, multiple in 25%	ACL repair in 27 of 213 patients (13%)	'Average of two prior surgeries per affected knee'
Richardson *et al.*, 1999[46]	B	2	30	NS	MFC involved in 100% of patients	NS	NS
RJAH Orthopaedic and District Hospital NHS Trust data[65 a]	A	49	35	3.9	Femoral condyles involved in ~38 of 49 (78%), OCD in ~11 of 49 (22%)	NS	85% of patients had two previous 'arthroscopic surgeries' that failed
Scorrano, 1998[63]	B	25	37	9.8	MFC involved in 70%, LFC in 11%, patella in 18.5% 'Pre-arthritic degenerative change' in 8 of 25 patients (32%)	NS Pins used in ACT	NS
Spalding *et al.*, 2000[64]	B	12	32	4.2	9 of 12 lesions (75%) purely chondral, 25% osteochondral	NS	NS
Verigen MACI data[66 b]	B	25	37	5.6	MFC involved in 12 of 25 (48%), LFC in 1 of 25 (4%), retropatellar in 6 of 25 (24%), combined in 6 of 25 (24%)	NS	All patients were treated surgically in the past (no details provided)
Verigen ACT data[67]	C	67	31	5.4	NS	NS	NS

MFC, medial femoral condyle; LFC, lateral femoral condyle; NS, not specified

[a] *Data collated from studies described in the industry submission by the RJAH Orthopaedic and District Hospital NHS Trust*

[b] *MACI refers to an implantation technique in which cells are cultured in a collagen biomatrix*

proportion of patients with full-thickness cartilage defects and need for concomitant surgery). Patients often receive multiple interventions for knee injury, making assessment of a particular intervention difficult and creating uncertainty when comparing different studies. No available study of ACT included concurrent or historical controls. Only one study of comparator treatments included controls (Hubbard).[30]

Few studies report follow-up beyond 2 years. Key studies reporting follow-up times of 2 or more years for ACT and comparator treatments are shown in *Table 5*.[13,30,36,42,61,68–72] Overall, 71–77% of patients treated with ACT reported a good or excellent outcome at 2 years. For comparator treatments, the range was 10–95%. This wide range for comparator treatments likely reflects differences in patient characteristics rather than treatment effect, but may also reflect variations in postoperative rehabilitation.

General remarks

Of the three best-quality reports, one was a voluntary patient registry maintained by Genzyme Tissue Repair and updated annually. The report for 1999 was obtained from Genzyme when preparing

TABLE 3 *RCTs currently in progress*[a]

Study type/location (lead researcher)	Patient numbers and interventions
Multicentre study based in the USA	300 patients: 150 to receive ACT (Carticel) and 150 to undergo subchondral drilling/microfracture
Multicentre study based in the USA	80 patients: 40 to receive periosteal graft without chondrocytes and 40 to receive ACT (Carticel)
Malmoe University, Sweden	60 patients: 20 to receive periosteal graft without chondrocytes, 20 to receive ACT (in-house technique) and 20 to undergo debridement
Göteborg, Sweden (Brittberg M)	60 patients: 30 to undergo subchondral drilling with periosteal flap and 30 to receive ACT
Norwegian study (Knutsen G)	80 patients: 40 to receive ACT and 40 to undergo microfracture
Multicentre study based in Denmark (Joergensen U)	Comparison of ACT, debridement and osteochondral graft (mosaicplasty) for lesions smaller than 2 cm^2
Single-centre randomised controlled study based in the UK (Bentley G, Royal National Orthopaedic Hospital, London)	68 patients, to date, have completed 1-year review: ACT compared with mosaicplasty
Lübeck, Germany (Behrens P)	100 patients: MACI versus microfracture
Siegsle, Denmark (Jacobsen B)	40 patients: MACI versus microfracture
European study based in Austria, Italy and Germany	300 patients: MACI versus other treatments, including mosaicplasty and microfracture

[a] *Sources: McGinn S, Carticel project manager UK, Genzyme Tissue Repair, Haverhill, UK; Giannetti B, Verigen, Leverkusen, Germany; and Bentley G, Royal National Orthopaedic Hospital, Stanmore, London, UK*

a report for the West Midlands Development and Evaluation Service (DES).[73] Data from Peterson and colleagues[61] were made available by the authors at the same time and have been published recently. The third report describes data on 20 patients followed for more than 1 year.[45] In this study, all patients improved, and only minor adverse effects (knee effusions) were reported postoperatively. However, patient characteristics were not described in detail. For example, details of previous surgeries or additional procedures required at the time of ACT were not given. Selection bias (how and why a particular individual was selected for ACT) and performance bias (greater care and attention being devoted to postoperative rehabilitation or psychological needs) are particular concerns with all available studies of ACT.

We attempted to express outcome data as an 'effect size' in order to allow comparisons between studies. However, the data proved to be uninformative because most outcome data for ACT and comparator treatments in these case series, when presented as effect size (as defined by Kazis and colleagues[74]), showed a value greater than 1.0, suggesting a large effect of treatment. In addition, we were concerned that outcome indices such as the Lysholm score for knee function (appendix 4) could not be regarded as a continuous variable, which is a prerequisite for calculation of effect size. This question raised further uncertainty about the utility of effect size. In view of this, we felt that comparisons of studies on the basis of effect size were inappropriate.

Cartilage Repair Registry, Genzyme Tissue Repair, 1999[42]

The Cartilage Repair Registry[42] is a voluntary registry. One obvious hazard of a voluntary database is that surgeons with poor results cease or decline to contribute data, therefore biasing results. It is unclear how many surgeons who utilise the services of Genzyme Tissue Repair do not contribute data to the registry. This registry provides data on more than 1500 patients, with a mean age of 35 years (range, 15–55 years). Follow-up of up to 3 years is reported, but only for 35 patients. Nearly a third of the reported knee problems arose from sporting activity, and approximately a quarter each resulted from falls or daily activity. The duration of symptoms preceding the ACT procedure is not reported. However, 49% of patients had been treated with debridement and lavage in the 5 years before ACT, and 28% by a marrow stimulation technique. About 29% of the patients did not

TABLE 4 *ACT studies included: clinical outcomes*

Study	*n*	Minimum follow-up	Clinical outcome	Adverse effects and need for further surgery
Bahuaud *et al.*, 1998[50]	24	≥ 6 months	Clinician assessment: – improved in 23 of 24 patients (96%) – poor in 1 of 24 patients (4%)	Algodystrophy: 2 of 24 patients (8%) Phlebitis: 1 of 24 patients (4%)
Burkhart *et al.*, 1998[51]	7	3 months	Lysholm score (100, best; 0, worst): – preoperative, 81 – postoperative, 91	None reported
Cartilage Repair Registry, 1999 (1 year)[42]	485	12 months	Clinician global assessment: – good/excellent in 78% (379 of 484 patients) – fair/poor in 22% (105 of 484 patients) Patient global assessment: – good/excellent in 77% (364 of 473 patients) – fair/poor in 23% (109 of 473 patients) **Other outcomes** — **Preop (SD)** — **Postop** Clinician global assessment (2, poor; 10, excellent): 3.5 (1.4) — 6.2* Patient global assessment (2, poor; 10, excellent): 3.2 (1.5) — 5.7* Pain (0, severe; 10, normal): 2.9 (2.1) — 5.7* Knee giving way fully (0, severe; 10, normal): 6.8 (3.4) — 8.4* Knee swelling (0, severe; 10, normal): 4.2 (2.8) — 7.0* * $p < 0.001$	Reported for 1896 patients in registry 'Treatment failure': 1.5% (cumulative rate, 4.7% at 3 years) 'Clinically relevant' adverse events: 9.9% Adhesions, hypertrophic change or loose body: 5.2% Detachment, delamination or periosteal tear: 2.4% Haematoma, synovitis or effusion: 1.4% Wound infection, cellulitis or lymphangitis: 0.7% Infection of bone graft, donor site, pin tract or joint, or avascular necrosis: 0.3% DVT or pulmonary embolus: 0.3% Increased knee pain: 1% More surgery (one or more procedures): 8.6% (reimplantation, further cartilage procedure, knee replacement or patellectomy in 1.3%)
Cartilage Repair Registry, 1999 (2 years)[42]	226	24 months	Clinician global assessment: – good/excellent in 77% (173 of 226 patients) – fair/poor in 23% (53 of 226 patients) Patient global assessment: – good/excellent in 72% (162 of 225 patients) – fair/poor in 28% (63 of 225 patients) **Other outcomes** — **Preop (SD)** — **Postop** Clinician global assessment (2, poor; 10, excellent): 3.4 (1.2) — 6.3* Patient global assessment (2, poor; 10, excellent): 3.2 (1.4) — 5.8* Pain (0, severe; 10, normal): 3.2 (2.1) — 5.9* Knee giving way fully (0, severe; 10, normal): 6.3 (3.6) — 8.0* Knee swelling (0, severe; 10, normal): 4.2 (2.8) — 6.9* * $p < 0.001$	See Cartilage Repair Registry above for data after 1 year Data specific for 2 years shown below Increased knee pain: 1.7% ***Reoperation procedures*** Arthroscopy, including debridement, lavage, loose body removal, partial implant removal, synovectomy, meniscus procedures, ligament repair and plica resection: > 11.4% Total knee replacement: 0.5% Osteochondral autograft: 0.3% Subchondral drilling: 0.4% Repeat ACT: 0.4% Abrasion arthroplasty: 0.1%
Erggelet *et al.*, 1998[52]	10	> 12 months	Cincinnati score (1, worst; 10, best): – preoperative, 3.6 – postoperative, 8.2	Not reported
Georgoulis *et al.*, 1998[53]	12	6 months	Improvement of pain: 100% of patients Return to work at 6 months: 100% of patients	Postoperative effusion: 1 of 12 patients (8%)

continued

TABLE 4 contd *ACT studies included: clinical outcomes*

Study	*n*	Minimum follow-up	Clinical outcome	Adverse effects and need for further surgery
Gillogly *et al.*, 1998[54]	25	12 months	Overall patient/clinician assessment (Cincinnati): – good to excellent in 22 of 25 patients (88%) **Other outcomes** **Preop** **Postop** Cincinnati score (1, worst; 10, best) – clinician assessment 3.3 6.8* – patient assessment 3.2 6.7* Pain (range, 0–10) 3.9 7.8* Swelling (range, 0–10) 4.3 8.1* Knee Society score (range, 0–100) 67 89* Sports score (range, 0–100) 38 66* * $p < 0.001$	None reported Need for further surgery in 3 of 41 patients (7%): one patient underwent debridement for hypertrophy, and two underwent arthroscopic lysis of adhesions
Hart and Paddle-Ledinek, 1998[55]	16	9 months	Clinician assessment: 100% of patients exhibited improved function and pain Second-look arthroscopy: 7 of 17 lesions (53%) in 13 patients had acceptable appearance Synovitis: improved in 100%	One patient with effusion at 9 months Need for further surgery in 1 of 16 patients (6%)
Knutsen *et al.*, 1998[56]	12	–	**Outcomes** **Preop** **Postop** Cincinnati score 3.0 6.6* Patient global assessment 3.3 5.6* Physician global assessment 3.0 6.1* * $p < 0.001$	None reported
Koh *et al.*, 1998[57]	26	16 months (mean)	**Outcomes** **Preop** **Postop** ***p*-value** Pain (range, 0–10) 2.7 4.4 0.005 Tegner score 1.5 2.1 0.1 Clinician global assessment 3.5 4.8 0.01 Patient assessment (range, 0–10) 3.5 4.6 < 0.05	None reported Need for further surgery in 11 of 26 patients (42%): the 18 required operations included osteotomy in two patients and total knee replacement in one patient
Löhnert *et al.*, 1999[45]	20	≥ 12 months	Cincinnati score (global): – preoperatively, all 20 patients were fair or bad – postoperatively, all 20 were good or very good **Other outcomes** **Preop** **Postop** Lysholm score 21.4 91.3 HSS score 44 90.5 Tegner score 1.5 4.5 DGKKT (0, worst; 100, best) 22.3 90.5 MRI scans 6 months postoperatively: 100% of defects filled	DVT or infections: none Knee effusions: 3 of 60 patients (one requiring aspiration)
McKeon *et al.*, 1998[58]	23	13 months (mean)	Clinician assessment: 100% of patients exhibited improved pain and function Second-look arthroscopy in 3 of 23 patients: all acceptable	None reported

continued

TABLE 4 contd *ACT studies included: clinical outcomes*

Study	*n*	Minimum follow-up	Clinical outcome	Adverse effects and need for further surgery
Minas, 1998[59,60]	44	12 months	**Outcomes** **Preop** **Postop** ***p*-value** SF-36 scales – physical function 33.3 41.5 < 0.05 – mental function 49.3 51.6 0.65 – social function 57.1 81.3 < 0.001 Knee Society score 114 141 < 0.001 WOMAC 35 24 < 0.05 Five of eight SF-36 scales (i.e. physical function, role-physical, bodily pain, vitality and social function) had significantly increased 1 year postop ($p < 0.05$) Patient global assessment: – improved in 72% of patients – same or worse in 28% of patients	Data from presentation abstract only 'Treatment failure': 5 of 70 patients (7%) Periosteal hypertrophy: 10% 'Incomplete integration': 11% Need for further surgery in 26 of 70 patients (37%)
Peterson *et al.*, 2000[61]	101	≥ 24 months	**Outcomes** **Good/excellent *n* (%)** **Fair/worse *n* (%)** Clinician global assessment – all patients (*n* = 101) 71 (71%) 25 (25%) – FCs/OCD (*n* = 59) 52 (88%) 7 (12%) – patella/multiple (*n* = 34) 20 (59%) 14 (41%) Patient global assessment – all patients (*n* = 93) 73 (79%) 20 (21%) – FCs/OCD (*n* = 59) 50 (85%) 9 (15%) – patella/multiple (*n* = 34) 23 (68%) 11 (32%) ***FCs/OCD group only* (n = 59)** **Outcomes calculated** **Preop** **Postop** ***p*-value** Lysholm score (0, worst; 100, best) 47 80 < 0.005 Cincinnati score (0, worst; 100, best) 32 58 < 0.005 Noyes score (0, worst; 10, best) 1.4 8.2 < 0.001 Brittberg–Peterson score (0, best; 130, worst) 75 23 < 0.005 Wallgren–Tegner score (0, worst; 15, best) 6.7 9 Second-look arthroscopy (> 2 years post-operatively, for FCs/OCD group; *n* = 53): acceptable in 57%, unacceptable in 23%	Haemarthrosis: 2% Superficial infection: 3% Fever: 1% Graft failure: 7 of 101 patients (7%) Need for further surgery in 21 of 101 patients (21%)
Peterson *et al.*, 2000[62 a]	213	≥ 24 months	**Outcomes** **Good/excellent % of patients** **Same/worse % of patients** Cincinnati score – all patients (*n* = 213) 78% 22% – FC (*n* = 84) with or without ACL repair 84% 16% – OCD (*n* = 32) 84% 16% – patella (*n* = 32) 69% 31% – multiple (*n* = 53) 75% 25% Of 31 patients with good outcomes at 2 years, 96% of these still had good outcomes at 5–10 years Second-look arthroscopy (*n* = 46): mean Brittberg score of 10.5 out of 12	See Peterson *et al.*[61] above – no additional data in abstract

[a] *Data shown here from abstract by Peterson* et al.[62] *are likely to include results of some patients shown above in published report by Peterson* et al.[61]

continued

TABLE 4 contd *ACT studies included: clinical outcomes*

Study	*n*	Minimum follow-up	Clinical outcome	Adverse effects and need for further surgery
Richardson *et al.*, 1999[46]	2	12 months	Lysholm score: – preoperative, 53.5 – postoperative, 66	Not reported
RJAH Orthopaedic and District Hospital NHS Trust data[65]	49	12–24 months	**Outcomes** **Preop** **Postop (1 year)** **Postop (2 years)** Lysholm score (range, 0–100) 48.9 73.3 78.4	One failure needing total knee replacement Debridement: 2 patients Wound infection, DVT, nodule in scar: 1 patient each Detachment of periosteal patch: 2 patients Periosteal patch adherence preventing cell implantation: 1 patient Failure to culture cells: 8 of 62 biopsies (13%)
Scorrano, 1998[63]	25	–	Cincinnati score: – good/excellent in 24 of 25 patients (96%) – fair in 1 of 25 patients (4%)	No adverse events No data on need for further surgery
Spalding *et al.*, 2000[64]	12	≥ 6 months	Global assessment: – improved in 10 of 12 patients (83%) – same in 2 patients (17%) Functional level (ICRS, 4-point scale): – improved by > 1 level in 6 patients **Other outcomes** **Preop** **Postop** ***p*-value** 'Modified' Cincinnati score 4.0 7.5 0.05 Lysholm score (0, worst; 100, best) 39.6 82.4 – Mohtadi QoL score 25.8 46.7 0.05 Second-look arthroscopy: normal in 4 of 6 patients (67%)	Debridement: in 2 of 6 patients subjected to arthroscopy No other adverse effects reported
Verigen MACI data[66]	25	18 months (mean)	'Overall improvement': 23 of 25 patients (92%) Unchanged: 1 of 25 patients (4%) Symptoms needing arthroscopy: 1 of 25 patients (4%) **Other outcomes** **Preop** **Postop** ***p*-value** Meyers score 4.0 7.5 0.05 Lysholm score (0, worst; 100, best) 63.2 85.9 0.05 Tegner score 3.6 6.1 0.05	Not reported One patient required arthroscopy within 3 months
Verigen ACT data[67]	67	–	64 of 67 patients (96%) 'expressed extreme satisfaction', 'pain ceased', 'normal work or sports activity performed' 3 months after surgery	Second-look arthroscopy: 'necessary' in 3 of 67 patients, all because of increased symptoms

Preop, preoperative; SD, standard deviation; postop, postoperative; DVT, deep venous thrombosis; HSS, Hospital for Special Surgery; DGKKT, deutsche Gesellschaft für Knorpel- und Knochenzelltransplantationen; WOMAC, Western Ontario and McMaster Universities osteoarthritis index; FC, femoral condyle; ICRS, International Cartilage Repair Society; QoL, quality of life

appear to have had any other surgical procedures prior to ACT. The average size of defect was 4.3 cm^2, and 76% of defects were of full thickness. During the two surgical procedures required for ACT, up to 20% of the patients also had meniscus surgery, 10% ligament surgery, 17% fragment reattachment or removal, 2.4% tibial osteotomy and 6.3% patella realignment.

One year after surgery, 77% of patients graded outcome as good or excellent, and 23% as poor or fair (data for 473 patients). The percentages at 2 years were 72% and 28%, respectively (data for 225 patients). Clinicians tended to rate results more favourably than patients. Specific assessments of knee pain and swelling also showed 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 arthroscopy. The need for additional surgery increased with longer follow-up. Failure of

TABLE 5 *Summary of key outcomes in reports with follow-up of at least 2 years*

Study	Follow-up (years)[a]	*n* (maximum)	Good or excellent outcome	Need for > 1 additional surgical procedure
ACT				
Cartilage Repair Registry, 1999[42]	≥ 2	226	77%	11.4%[b]
Peterson *et al.*, 2000[61]	≥ 2	101	71%	21%
Other interventions				
Aichroth, 1971[68] (mixed)	13[c]	105	63%	13%
Drongowski *et al.*, 1994[69] (arthroscopy with or without drilling)	4.3[c]	99	10%	Not reported
Hangody *et al.*, 1998[36] (mosaicplasty)	≥ 3	57	95%	3.5%
Hubbard, 1996[30] (debridement)	5	32	59%	Not reported
Hubbard, 1996[30] (lavage)	5	26	12%	Not reported
Hughston *et al.*, 1984[70] (mixed)	≥ 2	83	82%	≥ 4%
Linden, 1977[13] (mixed)	≥ 25	58	24%	Not reported
Lorentzon *et al.*, 1998[71]	≥ 2	26	96%	Not reported
Maletius & Messner, 1996[72] (with or without meniscectomy)	12	42	62%	24%

[a] *Median number of years, unless indicated otherwise*
[b] *Although the overall figure for reoperation was reported as 8.6%, this figure increased with time. Therefore, by 2 years, 11.4% of patients had had at least one operation, and by 3 years, this figure was 13.6%*
[c] *Mean number of years*

treatment, defined as a need for further surgery for the same defect (due to symptoms or loss of the graft), increased in time. Failure occurred in 1.5% of patients at 1 year, 3.2% at 2 years and 4.7% at 3 years. Total knee replacement was required in 0.5% of patients, and 1.5% required a marrow stimulation technique, further ACT procedure or osteochondral graft. Increased postoperative knee pain was noted by 1% of patients, and 0.3% experienced a deep venous thrombosis or pulmonary embolism.

Peterson and colleagues, 2000[61]

This case series report by Peterson and colleagues[61] described up to 101 patients with an average age of 30 years. Most patients were followed for at least 2 years. Twenty-one patients sustained injuries that were clearly related to sport. Most of these were twisting knee injuries. Symptoms had been present for a mean of 4 years prior to ACT, and approximately 83% of the patients had undergone at least one previous surgical procedure. Thus, about 17% of the patients had not had any prior surgical procedure. The average defect size was 4.3 cm^2, and all cartilage defects were of full thickness. Additional procedures performed at the time of ACT included ligament repair for 16% of patients. Details of other procedures, such as meniscus surgery, were not provided. The authors stated that the technique of treating patellar lesions was modified with experience, in that patellar defects received more radical debridement of diseased cartilage, in addition to patellar realignment when necessary. It was noted that Minas was a co-author of this report. Minas has also reported data independently (*Table 4*),[59,60] and it is unclear whether patients from his series have been included in this larger series.

Outcomes were reported in various subgroups according to the site of cartilage loss. After at least 2 years, 79% of patients graded outcome as good or excellent, and 21% graded outcome as poor or fair (data for 95 patients). Arthroscopic appearances postoperatively were described as acceptable in 57% of patients. A further surgical procedure (requiring at least an arthroscopy) was carried out in approximately 21 patients (21%), and seven of 101 grafts (7%) failed. Examination of subgroups shows that clinicians judge the outcome to be more favourable in patients with defects in femoral condyles (88% good or excellent) than in patients with defects in the patella (59% good or excellent). Further follow-up of this series of patients, reported in an abstract presented to the American Academy of Orthopaedic Surgeons, confirmed these

figures in 213 patients.[62] The authors further suggested that patients with good outcomes at 2 years continue to do well with longer follow-up times.

Other surgical treatments

The effectiveness of other interventions for knee cartilage defects have also been reported primarily as case series. No systematic reviews of other surgical treatments for knee cartilage defects were found. Case series described treatment in very different types of patients. For example, Blevins and co-workers[75] reported only on athletes, all with full-thickness cartilage defects, while in other reports, only 10% of patients had full-thickness cartilage loss. Patient age varied between a mean of 26 years and over 50 years in these series, and some studies clearly included a proportion of patients with well-established OA.[34] There was also heterogeneity in the sorts of treatments used and types of injuries or knee problems treated. For example, variations in the numbers of patients with concomitant injuries, such as ACL ruptures or injuries of menisci, may influence the outcomes reported.[72] Thus, there is a real concern that like is not being compared with like.

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 have been evaluated in controlled studies. For example, Hubbard's randomised open study is the only identified report of cartilage defects that was found to include a group of concurrent controls.[30] This study reported on older individuals with cartilage defects, of uncertain severity, on the medial femoral condyle, which is a site believed to have a favourable prognosis. Hubbard reported that 19 of 32 patients (59%) who had their cartilage defect debrided were pain-free after 5 years, compared with three of 26 patients (12%) treated by knee lavage only.[30] Finally, postoperative rehabilitation varies substantially. Patients treated with ACT have a prolonged and intensive postoperative rehabilitation that is not often matched with other treatments. Lorentzon and colleagues,[71] reporting on the use of a periosteal flap (without chondrocytes) in 26 patients followed for at least 2 years, showed good or excellent results in 25 patients (96%). Postoperative rehabilitation included CPM, and particular care was taken with weight-bearing. In this study, the subchondral bony plate was breached to allow marrow cells to have access to the cartilage defect, and biopsies in five patients showed hyaline-like cartilage.

Short-term outcomes, up to 3 years, are mostly favourable for a variety of treatments, including marrow stimulation techniques (drilling and abrasion), removal or refixation of loose fragments, mosaicplasty and debridement. Trials have reported good or excellent results in 10–96% of patients (*Table 5*). Patients treated with rib perichondrial grafts did not do well; only 38% had a good or excellent outcome 14 months after treatment.[34]

Few reports described follow-up beyond 3 years, and most were older publications reporting on patients with OCD. Linden[13] found that OA developed in most adults with OCD who were followed for at least 25 years. Aichroth[68] followed 105 patients for an average of 13 years and found that 63% had good or excellent function, with or without surgical intervention. 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, and 19% of patients in the series of Peterson and colleagues[61] had OCD. Most studies of OCD include relatively young patients, and such individuals have a greater capacity for cartilage repair.[12] The only long-term follow-up study of patients with a cartilage defect, diagnosed at arthroscopy, is a report by Maletius and Messner.[72] In this study, of 42 patients, 62% had good or excellent outcomes after at least 12 years of follow-up, although only 12% of the patients had a full-thickness cartilage defect.

Mosaicplasty appears to produce exceptional results, with 95% of patients returning to normal activity.[36] Some clinicians believe that this technique is feasible only for patients with smaller cartilage defects, but others believe that it is suitable for most commonly seen cartilage lesions (Bentley G, Royal National Orthopaedic Hospital, Stanmore, London: personal communication, 2000). However, patient populations who receive ACT and those who are treated by mosaicplasty may not be comparable, at least in the published literature. Both treatments use normal cartilage from within an abnormal joint to repair damaged cartilage, resulting in a new cartilage defect created by the surgeon. The areas from

which such cartilage is removed are regarded as unimportant for weight-bearing and knee function. However, a recent report, based on the examination of cadavers, showed that these areas are subject to significant contact pressure.[76] 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 were described poorly. Indeed, the studies of ACT provided a more complete description of adverse effects.

Chapter 3
Economic analysis

Summary of literature

Two studies examining the costs of ACT were identified (Minas,[60] and Lindahl and co-workers[77]). Neither study, however, compared ACT with any other treatment nor reported UK costs, because both studies were based abroad. However, for comparison, estimated current UK costs (see appendix 5) are shown in parentheses.

Minas,[60] in a study based in Boston, calculated direct in-hospital costs. He assumed that all costs were incurred during the first year after ACT. He cited costs from a variety of US sources and reported the 1997 cost of ACT to be in the range of US$17,607 (£12,649, based on all sterling costs inflated to year 2000) to $38,400 (£27,587), with a mean of $26,769 (£19,231). Minas reported the cost of ACT at his institution to be $29,000 (£20,834). Lindahl and co-workers,[77] in an unpublished paper, provided Swedish costs. The cost of ACT, including the cost of cell culture, was SEK100,000 (£7725) in 1998. Rehabilitation after ACT cost an additional SEK81,377 (£6286). Arthroscopy was reported to cost SEK10,000 (£773), and rehabilitation after arthroscopy cost SEK13,500 (£1043).

In a cost model, Lindahl and co-workers[77] compared work absenteeism and direct medical costs in the 10 years prior to ACT with the projected costs 10 years after ACT. Fifty-seven patients were included, and the costs of further surgery were considered. In their model, the authors estimated that each patient had a mean of two surgical procedures in the 10-year period before ACT, at a cost of SEK47,000 (£3631). They also estimated that each patient lost 1550 days from work during this time, at an estimated opportunity cost of SEK982,457 (£75,895). In the 10-year period after ACT, patients were estimated to have 0.3 surgical procedures, at an estimated cost per patient of SEK7050 (£545). Work absenteeism was estimated to be 15 days per patient, at an estimated opportunity cost of SEK9508 (£735). The authors calculated that ACT leads to a real cost saving of 1998 SEK705,166 (£54,474) after surgery. The saving in terms of medical care was not reported separately from absenteeism. It would appear that the cost saving is the result of very large savings in absenteeism and, to a much lesser extent, medical care.

In sensitivity analyses, Lindahl and co-workers[77] estimated that the threshold for equal costs occurred if the reoperation rate after ACT was 18% per annum and if work absenteeism exceeded 28 days per annum. The authors estimated a requirement for additional surgeries in the 10 years after ACT for their base analysis (0.3 surgical procedures per patient). Their analysis is sensitive to this assumption, and because there are no reliable data on outcome 10 years after ACT, their estimates should be treated with caution. The authors also used a 3% discount rate and did not provide details of when costs are incurred with the flow of time. Thus, it is difficult to adjust costs to the UK Treasury-recommended discount rate of 6% for costs.

Minas[60] reported Medical Outcomes Short Form with 36 Items (SF-36) data for 43 patients treated with ACT. However, no data were reported for comparator treatments because the study lacked a control group. No other studies of ACT reported health status using a generic health status instrument. Minas reported that, 12 months after surgery, patients showed improved SF-36 scores on five domains, including physical functioning, role-physical, bodily pain, vitality and social functioning, compared with baseline values. For example, the physical component score improved from 33.3 to 41.5 ($p < 0.05$) and the social functioning score from 57.1 to 81.3 ($p < 0.001$). Minas also reported data on cost per quality-adjusted life-year (QALY) in his report. However, it is unclear how these data were obtained. This report fails to meet appropriate standards for economic evaluations,[78] and the reported cost per QALY is thus unreliable.

In the absence of any UK estimates of costs and cost-effectiveness, we developed our own model. Details are provided below (see *Modelling and assumptions*).

Genzyme, as described in their submission to NICE (section 5, page 74),[79] conducted an analysis of cost and cost-effectiveness for the treatment

of cartilage defects in knees. In order to perform this analysis, the authors sought the opinions of experts (four surgeons) in a detailed survey. The estimated cost profiles are a fair reflection of the true costs and are similar to those estimated below (see *Estimation of costs and benefits*). The total costs of ACT were estimated by Genzyme to be £9532 (inflated to year 2000), with a cell culture cost of £6499. Genzyme also provided QALY estimates, derived from raw SF-36 data reported by Minas.[59] The Genzyme report[79] described the transformation of SF-36 data into health utilities using a model that is regarded by its author as developmental and preliminary.[80] On this basis, we believe that the data presented in the Genzyme report cannot be considered reliable. No quality-of-life data were reported for comparator treatments. Instead, this report described the use of clinical scenarios to derive QALY values. In doing so, the 1-year health utility estimate is assumed to remain constant for 20 or 40 years. We believe this highly optimistic scenario assumes an unrealistic estimate of the clinical effectiveness of ACT.

Methods for economic analysis

The goal of our economic analysis was to synthesise the costs and effectiveness evidence for ACT, versus other procedures, using available data. In view of the limited effectiveness data, especially limited follow-up time, we restricted our analysis to the limits of the effectiveness data. Thus, we considered a time horizon of 2 years from treatment. It is clear, however, from studies of OCD (e.g. Linden,[13] *Table 5*) that this limited time horizon is inadequate. In order to project beyond 2 years, many assumptions are required.[81] For example, assumptions about the possible superior durability of ACT, and therefore a lesser need for total knee replacement, compared with other treatments, are required.[81] In view of the uncertainties involved in making such assumptions, a longer time horizon has not been included in this report. Our report to the West Midlands DES committee, however, described a 10-year time horizon with the many assumptions required in conducting this analysis.[73]

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 published literature, data from the Royal Orthopaedic Hospital in Birmingham, a recent survey of 11 NHS Trusts,[82] unpublished Swedish data,[77] as well as manufacturer and national sources (see appendix 5 footnotes). Mean costs were calculated when data were available for comparable procedures. Costs occurring in the second year were inflated at 4% to take into account medical sector inflation. All figures reported in the text were for the year 2000 and are discounted at 6%, unless stated otherwise.

Modelling and assumptions

For our economic analysis, we used a decision tree model. The model adopted is shown in *Figure 2*. In the absence of detailed data, more complex modelling techniques have not been used. Our decision tree considers ACT versus any other surgical therapeutic option. Descriptions of the indications for ACT, and the choice and nature of other therapies are described in earlier sections (see *Treatment options*, and *ACT: indication, diffusion and potential costs*). We have assumed that, because cartilage defects are most likely to be diagnosed at arthroscopy, most individuals with a defect would undergo at least knee lavage. Patients would probably also have a debridement procedure at arthroscopy (see study by Hubbard[30] in *Table 5*). Thus, the start point for our decision tree is a symptomatic cartilage defect after debridement. We have assumed that, if outcome is poor after debridement, patients who choose more surgery could be treated by a marrow stimulation technique, further debridement, mosaicplasty, carbon fibre implants or ACT. We believe this scenario captures likely current practice.

We sought details on costs and quality of life from the Health Economic Evaluation Database (Office of Health Economics), DARE, NHS EED, MEDLINE, EMBASE, the Science Citation Index and the HTA database (see *Search strategy* above). The search terms arthroscopy, athletic injuries, cartilage, fracture, knee, costs and quality of life were used. Searches using appropriate truncation terms were also used. Probabilities and costs were attached to the decision pathways. We were unable to attach health utilities to decision pathways because, unfortunately, no reliable quality-of-life data were available for ACT. Data were available for other knee disorders; however, in the absence of differences in clinical effect between treatments at 2 years, we considered it inappropriate to use these data.[26] Outcomes of ACT were dichotomised as 'poor' or 'good' (*Table 4*).

Assumptions in respect to clinical effects

Base case probability estimates for the clinical outcomes used in the decision tree are shown in *Table 6*. It was assumed that all failures would

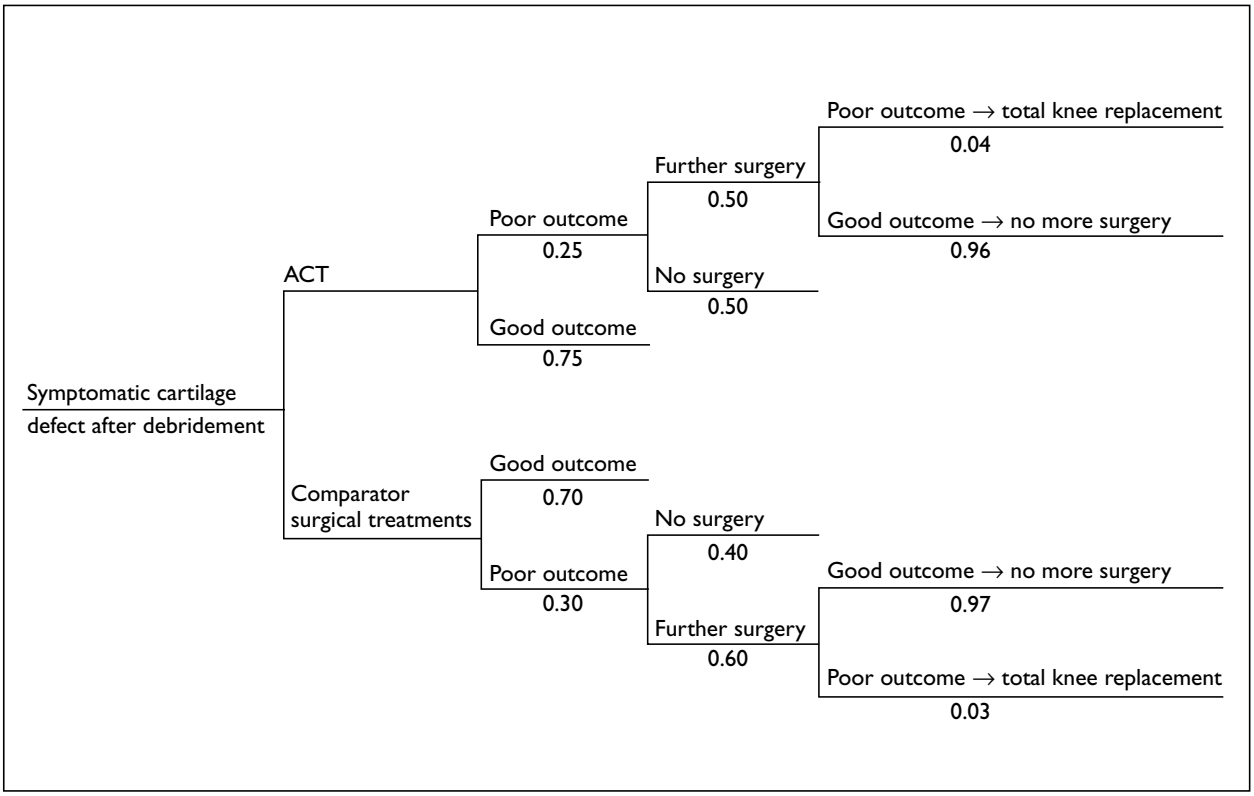

FIGURE 2 *Decision tree used for economic analysis: base case probabilities*

necessitate further surgery and that a proportion of patients would require total knee replacement in due course. Data from the Cartilage Repair Registry[42] indicate a failure rate of 3.2% after 2 years, while Peterson and colleagues[61] reported a failure rate of 7%. Satisfactory biological repair with ACT requires more than 6 months to occur and failures might be expected, while hyaline cartilage is formed during the early months after surgery. Thus, the failure rate might be expected to plateau with time. Indeed, Peterson and colleagues[61] reported that failures occurred within 2 years and occurred more frequently during their early experiences with ACT, suggesting a learning effect for surgeons performing ACT.

For comparator treatments, at least one further surgical procedure was required for between 3.5% and 24% of patients (*Table 5*). In some cases, further surgery is carried out to remove hardware and not necessarily for symptoms. For ACT, 11–21% of patients require at least one further surgical procedure after 2 years of follow-up. We have assumed, for both comparator treatments and ACT, that further surgery is performed only in patients who have an initial poor outcome. Therefore, assuming that 25% of patients suffer a poor outcome after ACT at 2 years and that 50% of those with poor outcomes consent to further surgery, the overall probability of needing more surgery after ACT is estimated to be 12.5%. For comparator treatments, estimating the requirement for additional surgery is more difficult because this information is very poorly reported. The data summarised in *Table 5* indicate that a mean of 44% of patients have a poor outcome, in some cases after prolonged follow-up. Using this figure for guidance, we have assumed that, at 2 years, 30% of patients suffer a poor outcome after initial surgery and that 60% of these patients consent to further surgery. This estimate is based on Maletius and Messner's contemporary study[72] that describes arthroscopic interventions with prolonged follow-up. In this study, 24% of patients had further surgery and 38% had poor outcomes. Assuming that further surgery was undertaken only in patients with a poor outcome, the risk of further surgery, after a poor initial outcome, was calculated to be 63% based on these data.

In general, we have assumed an equivalent clinical effect, as indicated in our effectiveness review. This assumption may prove inaccurate in the light of further data. On the basis of a follow-up period of only 2 years and uncertainties regarding clinical effect, our analysis should not be construed as a cost-minimisation exercise.

TABLE 6 *Two-year probabilities for clinical outcomes*

	Probability over 2 years
ACT	
Good outcome, no more surgery	0.75 (worst case, 0.6; best case, 0.8)
Poor outcome, no more surgery	0.125
Poor outcome, more surgery, no TKR	0.12
Poor outcome, more surgery, TKR	0.005[a]
Comparator	
Good outcome, no more surgery	0.7 (worst case, 0.4; best case, 0.9)
Poor outcome, no more surgery	0.12
Poor outcome, further surgery, no TKR	0.17
Poor outcome, further surgery, TKR	0.005[b]

TKR, total knee replacement

[a] *Data from Cartilage Repair Registry*[42]

[b] *Data were adopted from ACT because there are no reliable estimates from studies of comparator treatments*

Estimation of costs and benefits

We compiled UK costs using available data. Direct comparisons of these costs with costs in the reports of Minas,[60] and Lindahl and co-workers[77] are not appropriate because of significant differences in the healthcare systems. Details of unit costs are shown in appendix 5, including any assumptions. Details of costs in clinical pathways are shown in appendix 6. Key costs are summarised in *Table 7*.

TABLE 7 *Summary of key cost data for ACT, including incremental costs*

	Cost (by supplier of cells)		
	Carticel	**Verigen**	**OsCell[a]**
Key costs			
Cells alone	£6500	£3000	£2000
Cells and surgery	£8167	£4667	£3683
Cells, surgery and rehabilitation	£8547	£5047	£4063
Incremental cost for full episode[b]	£7695	£4195	£3211

[a] *OsCell is the cell culture technique used by the RJAH Orthopaedic and District Hospital NHS Trust*

[b] *Cost of comparator treatments assumed to be £852*

Using detailed costs shown in the appendices, we estimate that, in a UK context, ACT will cost the NHS £4667 if Verigen supply cells and £8167 if Genzyme supply cells (Carticel). In addition, we estimate that rehabilitation will cost £380, giving a total cost for ACT of £5047 (with Verigen cells) or £8547 (with Carticel). Many of the alternative surgical treatments for cartilage defects can be performed as elective inpatient or elective day-case arthroscopic procedures. The costs of elective inpatient and elective day-case arthroscopy are £815 and £536, respectively. We estimate that rehabilitation after arthroscopy costs £316 in the UK, assuming that patients have, on average, three outpatient visits and ten sessions of physiotherapy. Thus, the total cost of an arthroscopic procedure is £1131 (for elective inpatient arthroscopy) or £852 (for elective day-case arthroscopy). Assuming that comparator treatments cost £852, the incremental full-episode cost of ACT versus alternative treatments would be £4195 (with Verigen cells) or £7695 (with Carticel).

This analysis does not include the financial cost to individual patients in terms of work incapacity or the costs of travel and time off work. Because there are no direct comparisons of ACT with other treatments in terms of effectiveness, we are unable to estimate, or comment on, other potential cost differences.

As part of their submission, the RJAH Orthopaedic and District Hospital NHS Trust[65] provided cost data for chondrocyte culture performed using their in-house facility (called OsCell). They estimate that OsCell costs £2000. However, their data show a failure to culture cells on eight out of 62 attempts (13%). Five of the eight patients had another arthroscopy to obtain more tissue for culture, while the other three were not treated with ACT. By incorporating failure rates, the cost of OsCell rises to £2161. Including surgical costs, we

estimate that the NHS cost of ACT performed using OsCell would be £3683, or £4063 when both surgical and rehabilitation costs are included. The RJAH Orthopaedic and District Hospital NHS Trust have suggested that the cost of cell culture would fall with higher volumes. A cell culture cost of £1800 was cited, if 60 patients are treated per annum, or £1400, if 100 patients are treated per annum. These estimates suggest a potential minimum cost to the NHS of approximately £3500 for ACT.

Sensitivity analysis

Sensitivity analysis was performed to consider the impact of changes in modelling inputs. In order to achieve cost equivalence between comparator and ACT arms, the comparator arm costs would need to rise by 540% (versus ACT with Verigen cells) or 950% (versus ACT with Carticel). Assuming that all patients in the comparator arm were treated by inpatient arthroscopy, rather than as a day case, the costs in the comparator arm would rise by 33%. It was difficult, on this basis, to imagine clinical scenarios in which the cost gap between ACT and comparator treatments for an average patient might be significantly reduced over a 2-year period. Therefore, we concentrated in sensitivity analysis on using the best- and worst-case estimates from the evidence review for initial response to ACT and comparator (*Table 8*). We conducted a one-way analysis using each of these estimates, as well as a two-way analysis of the most favourable scenario for ACT (i.e. best-case estimate of ACT and worst-case estimate of comparator) and similarly of the most favourable scenario for the comparator treatments.

Base case estimate

The base case estimate of expected incremental cost at 2 years was £3771 (with Verigen cells) and £7271 (with Carticel), as shown in *Table 8*. For OsCell (RJAH), this figure was £3167. Cell culture was the principal cost driver in the ACT arm. It accounted for 62% (Verigen cells) and 78% (Carticel) of expected costs. Sensitivity analysis suggested that incremental cost might range from £3500 to £4000 (with Verigen cells) and £7000 to £7500 (with Carticel). It might be possible to reduce this incremental cost difference by extending the time horizon and assuming that ACT produces better clinical outcomes compared with other therapies in the longer term. This might be the case, for example, if ACT led to a reduced requirement for total knee replacement or other clinical interventions. Such speculations, however, are not justified on the basis of available effectiveness data.

Adverse effects

Life-threatening adverse effects of surgery, such as severe infection and pulmonary embolism, have not been included in the decision analysis. This exclusion was justified on the grounds that such events are rare. They occurred, for example, in less than 1% of cases reported in the Cartilage Repair Registry.[42] However, ACT involves two surgical procedures (the first to harvest cartilage and the second for implantation after culture), compared with, for example, a marrow stimulation technique, which requires only one procedure. Potentially, for ACT, this difference represents a doubling of the risk of serious adverse events.

TABLE 8 *Base case and sensitivity analysis: incremental costs based on outcome probabilities*

Scenario	Incremental cost			
	Discounted		Not discounted	
	Carticel	Verigen	Carticel	Verigen
Base case	£7271	£3771	£7268	£3768
One-way analysis				
ACT: good outcome, 0.8; poor outcome, 0.2	£7239	£3739	£7234	£3734
ACT: good outcome, 0.6; poor outcome, 0.4	£7366	£3866	£7369	£3869
Comparator: good outcome, 0.9; poor outcome, 0.1	£7406	£3906	£7412	£3912
Comparator: good outcome, 0.4; poor outcome, 0.6	£7067	£3567	£7052	£3552
Two-way analysis				
Best case:				
ACT good outcome, 0.8; comparator good outcome, 0.4	£7035	£3535	£7018	£3518
Worst case:				
ACT good outcome 0.6; comparator good outcome, 0.9	£7502	£4002	£7513	£4013

Risk of failure

Finally, because ACT requires the culture of chondrocytes in a laboratory before implantation, there is a risk of failure with this process. This risk may vary with different providers of the chondrocyte culture service. A report from Genzyme indicated that only one out of 304 orders failed to meet release specifications.[48] 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 a patient is potentially subjected to an additional arthroscopy for procuring more tissue. Similar data from other providers of chondrocyte culture are not available, and it is not clear whether the Genzyme figures can be matched. Based on a small sample size, the RJAH Orthopaedic and District Hospital NHS Trust reported a failure to culture cells in 13% of cases.

Chapter 4
Discussion

The symptoms of hyaline cartilage defects in knees may vary from none to symptoms of pain, locking, giving way and knee swelling. Follow-up studies of patients with OCD, a defect of unknown aetiology that involves cartilage and bone, show that more than a third of these patients develop OA after 10 years or longer. In approximately 70% of patients, ACT improves symptoms assessed according to a patient-centred global outcome score. This improvement is sustained for a minimum of 2 years. Symptoms improve with other types of surgery, or no surgery, in a similar proportion of patients for similar periods of time, but less consistently.

For the purposes of this review, an assessment of cost–utility was not possible using a 2-year decision analytic model. The estimated base case cost of ACT was £5047 (with Verigen cells) or £8547 (with Genzyme Carticel), including the costs of surgery and rehabilitation. The costs of other types of knee surgery, performed during arthroscopy, were estimated to be £1131 (elective inpatient arthroscopy) or £852 (elective day-case arthroscopy). These costs assume a health service perspective.

Data presented to NICE indicate that 19 UK surgeons contributed data to the Cartilage Repair Registry (Genzyme Tissue Repair) and that 41 patients have been treated using Carticel in the UK (1999 data).[79] Data from the RJAH Orthopaedic and District Hospital NHS Trust[65] show that 62 patients have been treated using their in-house chondrocyte culture system. Fifty UK surgeons have participated in a worldwide training programme for ACT offered by Genzyme Tissue Repair. Industry submissions suggest that from 850 patients (RJAH[65]) to 2500 patients (Genzyme Tissue Repair[79]) per year might be referred for ACT. These estimates suggest a potential annual cost to the NHS of between £6.8 and £20 million, including cell culture, operative and rehabilitation costs (assuming an estimated cost of £8000 per procedure). However, if ACT is performed at the rates seen in the USA, where the procedure appears to be widely disseminated and where 1076 implants were performed in 1999 (USA population, 268 million), the annual cost of an ACT programme in the UK might be £2.2 million, as estimated by Genzyme. Verigen Transplantation Service International estimates that 22,000 patients per year might benefit from ACT.[67]

Researchers have stated that ACT is likely to provide a more durable repair of cartilage defects than other forms of treatment. This view is supported by histological data showing the formation of hyaline cartilage following ACT, as opposed to the fibrocartilage found in other circumstances.[83] Hyaline cartilage formation has also been reported without the use of chondrocytes.[71] This finding perhaps reflects the impact of differing postoperative rehabilitation. Because cartilage precursor cells may be found in periosteum and bone marrow, it is unclear whether the implantation of cultured chondrocytes is essential for hyaline cartilage formation. Whether newly formed hyaline cartilage proves to be durable and capable of integrating with surrounding unaffected hyaline cartilage in a human knee joint has not been established with certainty. Concerns remain that, regardless of the nature of repair tissue, bonding between newly formed tissue and neighbouring resident cartilage will remain imperfect and susceptible to failure.[18] Until patients have been followed for longer periods and until methods for examining cartilage structure and resilience by non-invasive means are developed, uncertainty will persist.

In assessing the outcomes of interventions, emphasis was given to an overall outcome. This measure was 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-outcome scoring systems into a global outcome. For example, the proportion of the same patients rated excellent by the Lysholm, Hospital for Special Surgery and Cincinnati knee scoring systems varies between 23% and 76% (appendix 4).[84] This variation 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 in this review by using a dichotomous classification of 'good' or 'bad' for outcomes and by exploring an adequate range

of outcomes in sensitivity analysis. Clinical outcome scores cannot be replaced by surrogate end-points, such as radiographs, because the relationship between cartilage loss seen at arthroscopy correlates poorly with the degree of change seen on a radiograph. Radiographs in turn correlate poorly with symptoms.[85]

A major factor influencing the assessment of all therapies for cartilage defects is that, in contemporary practice, most lesions have been identified through arthroscopic examination of knee joints. The natural history of these lesions is poorly understood. Thus, judging outcomes of any surgical intervention is fraught with uncertainty. It is presumed, largely on the basis of epidemiological studies of athletes who have sustained knee injuries and from long-term follow-up studies of OCD diagnosed on X-rays, that patients, particularly adults, with large full-thickness cartilage defects have a high risk of developing OA. Most of the studies identified in this report were case series with all the biases inherent in such studies. In addition, there was considerable patient heterogeneity. Also, patients often had multiple interventions to treat an injured knee joint, further complicating the assessment of a particular treatment. Some of these issues may be addressed by parallel group studies currently underway. However, it is unlikely that randomised studies over 10–20 years will be conducted, even though such timescales are required to determine critical outcomes relating to knee function. This obstacle should not be taken to imply that all RCTs are unfeasible. RCTs that extend for 2 years may provide key data, especially if an early response in RCTs can be predicted (from long-term observational data) to lead to a more sustained response. Therefore, observational studies of high quality and with long follow-up times will be needed to inform judgements on the effectiveness of ACT.

Chapter 5
Conclusions

On the basis of the available literature, no definite conclusions can be drawn about the clinical 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. The costs of ACT are substantial in comparison with other treatments, and surgeons using other treatments have reported clinical outcomes similar to those obtained with ACT. Because all 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, continued follow-up assessment from established case series remains the only source of useful data, with all the inherent uncertainties relating to this type of information.

Implications for other parties

Allowing for the limitations of the available data, no conclusions can be drawn about the relative impact of different surgical treatments on patients, carers, social services and employment agencies. We have not considered the social costs of poor knee function on loss of employment, particularly in patients with physically demanding jobs or, for example, in professional sportsmen and sportswomen. We also did not attempt to assess the impact of patient disability on families and the state. The impact of these factors, in the time frame considered in our economic analysis, does not appear to be substantially different for the various treatment options, including ACT. It is possible that, by extending the time horizon and assuming better outcomes are sustained with ACT but not with other therapies, financial and human costs might be less with ACT. Such speculations, however, are not justified until data from controlled studies become available.

Factors relevant to NHS

- The dissemination of ACT has arisen through a special interest in this procedure on the part of particular specialist knee surgeons. Specific surgical training has been given to the surgeons carrying out ACT. Thus, in the future, there is a need to establish surgical standards to ensure that ACT is used only for appropriate indications and by trained specialists.
- It is also important that patients give truly informed consent, in view of the limitations of the effectiveness data.
- ACT falls within the definition of a medicinal product, as set out in the European medicinal products legislation.* It is important to consider the biological safety of cultured chondrocytes. Quality assurance schemes for the use of somatic cells in therapy are not currently in place, although a draft European document was released for consultation in December 1999, with a deadline of June 2000 for receipt of comments. Key safety issues should be addressed in relation to the preparation and culture of chondrocytes in the laboratory, for use in humans.

Recommendations for research

- Further studies are required to provide more accurate data on the occurrence of cartilage defects. Such studies need to assess hyaline cartilage defects that arise acutely and those that are secondary to other types of knee injuries.
- The relationship of cartilage defects to clinical symptoms needs more detailed scrutiny.
- The natural history of cartilage defects diagnosed by modern arthroscopic methods should be evaluated in greater detail.
- Further clinical trials, for example, on appropriate comparators for ACT, should be guided by randomised trials currently in progress or planned (*Table 3*). Issues such as

* Referenced in: The European Agency for Evaluation of Medicinal Products. Points to consider on human somatic cell therapy. CPMP/BWP/41450/98. Directive 65/65EEC as amended, Directive 75/318/EEC as amended, Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03)

differences in outcome in patient subgroups should be addressed in prospective studies (e.g. the suggested poor outcomes in patients with patellar defects). Patients included in randomised trials should be followed for as long as possible.
- Deficiencies in evaluating the clinical outcomes of knee injury need to be addressed,[84] and measures of general health status need to be adopted more widely in all knee studies.
- Methodological research is required to address study designs, other than randomised trials, that might be used to address complex interventions such as those required in complex knee injuries.

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Appendix 1

Outerbridge classification system for cartilage defects[40]

Grade	Description
I	Softening or swelling of cartilage
II	Fragmentation or fissuring in an area 0.5 inches in diameter or less
III	Same as grade II but an area greater than 0.5 inches in diameter
IV	Erosion of cartilage down to bone

Appendix 2

Search strategies

		Number of citations
Terms used for MEDLINE search (1966 to 6 May 2000)		
1	exp arthroscopy/ or exp athletic injuries/ or exp cartilage, articular/ or exp knee injuries/ or exp knee joint/ or exp osteochondritis dissecans/ or exp patella/ or exp chondrocytes/	48,564
2	("osteochondral fracture" or "chondral fracture$").mp.	116
3	exp cartilage diseases/	2,767
4	"cartilage defect$".mp.	265
5	exp osteoarthritis, knee/su,th	130
6	or/1–5	50,396
7	exp cell transplantation/ or exp transplantation, autologous/	37,211
8	(chondrocyte transplantation or chondrocyte implantation or cartilage graft$).mp.	558
9	chondrocyte$.mp. and transplant$.tw.	277
10	chondrocyte$.mp. and implant$.tw.	225
11	(act or aci).tw.	60,828
12	or/7–11	98,632
13	6 and 12	1,021
14	limit 13 to human	621
Terms used for EMBASE search (1988 to 6 May 2000)		
1	exp knee/ or exp knee arthritis/ or exp knee arthrography/ or exp kneearthroscopy/ or exp knee disease/ or exp knee function/ or exp knee injury/ or exp knee instability/ or exp knee ligament injury/ or exp knee meniscus/ or exp knee meniscus rupture/ or exp knee osteoarthritis/	13,758
2	exp sport injury/	4,778
3	exp articular cartilage/ or exp cartilage/ or exp cartilage cell/ or exp cartilage degeneration/	12,319
4	exp osteochondritis dissecans/ or osteochondral fracture$.mp. or chondral fracture$.mp	497
5	exp chondropathy/ or chondropathy.mp.	8,546
6	or/1–5	34,812
7	exp cartilage graft/ or exp cartilage transplantation/ or exp cell transplantation/ or "autologous chondrocyte transplantation".mp.	4,210
8	chondrocyte$.mp. and transplant$.tw.	181
9	chondrocyte$.mp. and implant$.tw.	182
10	(act or aci).tw.	43,149
11	exp autotransplantation/	1,884
12	autologous chondrocyte implantation.mp.	7
13	or/7–12	49,221
14	6 and 13	839
15	Limit 14 to human	450

Appendix 3

Clinically relevant ACT reports

Citation	Included?	Reason for exclusion/ comment
Akeson, 1998[86]	No	Review article
Bahuaud *et al.*, 1998[50]	Yes	–
Barone, 1996[87]	No	Review article
Brittberg *et al.*, 1994[83]	No	Superseded
Brittberg *et al.*, 1995[88]	No	Review article
Brittberg, 1999[89]	No	Review article
Burkart *et al.*, 1998[51]	Yes	Abstract
Cartilage Repair Registry, 1999[42]	Yes	Voluntary patient registry
Chen *et al.*, 1997[90]	No	Review article
Erggelet *et al.*, 1998[52]	Yes	Abstract
Fricker, 1998[81]	No	News article
Georgoulis *et al.*, 1998[53]	Yes	Abstract
Gilbert, 1998[91]	No	Review article
Gillogly *et al.*, 1998[54]	Yes	–
Hart & Paddle-Ledinek, 1998[55]	Yes	Abstract
Jackson & Simon, 1997[92]	Yes	Review article
Josimovic-Alasevic & Fritsch, 1998[93]	No	Review article
Knutsen *et al.*, 1998[56]	Yes	–
Koh *et al.*, 2000[57]	Yes	Two abstracts found; latest cited
LaPrade & Swiontkowski, 1999[94]	No	Review article
Lindahl *et al.*, 1999[77]	No	Data duplication
Löhnert *et al.*, 1999[45]	Yes	–
McKeon *et al.*, 1998[58]	Yes	Abstract
Mandelbaum, 2000[95]	No	Suspicion of data duplication
Mankin, 1994[96]	No	Editorial
Mayhew *et al.*, 1998[48]	No	Data duplication
Messner & Gillquist, 1996[15]	No	Review article
Minas & Nehrer, 1997[97]	No	Review article
Minas, 1998[60]	Yes	–
Minas, 1996[98]	No	Review article
Minas & Peterson, 1999[41]	No	Review article
Mont *et al.*, 1999[44]	No	No relevant data
Nehrer *et al.*, 1997[99]	No	No relevant data
Pelinkovic *et al.*, 1998[100]	No	No relevant data
Peterson, 1996[101]	No	Data duplication
Peterson, 1998[102]	No	Data duplication
Peterson *et al.*, 2000[61,62]	Yes	One abstract
Richardson *et al.*, 1999[46]	Yes	–
Richardson, 1999[103]	No	Review article
Robert & Bahuaud, 1999[104]	No	Review article
Rudert & Wirth, 1997[105]	No	Review article
Thornhill, 1997[106]	No	Review article
Turgeon, 1998[107]	No	Suspicion of data duplication
Scorrano, 1998[63]	Yes	Abstract
Spalding *et al.*, 2000[64]	Yes	Abstract
Steinwachs *et al.*, 1999[108]	No	Review article

Appendix 4

Commonly used clinimetric scoring systems for assessment of knee disorders

Scale	Description
Lysholm score[109] (100, best; 0, worst)	Scores are obtained with patient collaboration. Items include limp, requirement for a support (e.g. crutch), stair-climbing, squatting, walking, running and jumping, pain, swelling and thigh atrophy
Noyes (Cincinnati) symptom rating scale[110] (10, best; 0, worst)	Six components of knee function are included in this rating system, including walking, stairs, squatting or kneeling, straight running, jumping or landing, and hard twists or cuts or pivots. For example, the combination of normal knee, the ability to work, and participation in sports involving jumping and hard pivoting would be graded 10 points, while severe unrelieved symptoms associated with activities of daily living would be graded 0 points. Symptoms that are rated include pain, partial giving-way and full giving-way. A sports rating scale (100–0 points), functional scale assessing daily living activity (120–0 points), sporting activity (100–0 points) and aspects of clinical examination (e.g. pivot shift test, degree of crepitus and range of motion) may also be incorporated into a detailed scheme to produce the final rating
Knee Society scoring system[111] (200, best; 0, worst)	The goal of this scoring system is to evaluate the outcome of knee arthroplasty. The system assesses pain, function (e.g. walking and stair-climbing) and clinical features (e.g. range of motion, stability, alignment, flexion contracture and extension lag). The assessment consists of two components: first, a knee rating system includes pain (50 points), stability (25 points) and range of motion (25 points); second, a functional assessment considers walking distance (50 points) and stair-climbing (50 points), with deductions for the use of walking aids
Hospital for Special Surgery rating scale[112] (100, best; 0, worst)	Scores are determined based on 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); and instability (10 points)
International Knee Documentation Committee[113] (100, best; 0, worst)	The following items are rated, according to the scale, as normal, nearly normal, abnormal and severely abnormal: patient assessment of function, symptoms, range of motion and ligament examination

Appendix 5

Unit cost estimates for year 2000

Source	Cost of individual item (£)										
	Orthopaedic outpatient follow-up visit	Primary TKR FCE	Knee MRI (per scan)	Arthroscopy (FCE)		ACT		Physio-therapy (per session)	Rehabili-tation (per episode)	Inpatient stay (per day)	CPM (per day)
				Elective day case	Elective inpatient	Cell culture alone	Cell culture plus surgery				
Bryan, 2001[82a]	52	–	146	530	832	–	–	52	–	–	–
ROH NHS Trust[b]	–	3,798	462	501	1,150	–	8,721	–	–	–	–
Minas, 1998[60 c]	–	–	–	–	–	–	20,834	–	–	–	–
Lindahl *et al.*, 1999[77 d]	–	–	–	–	773	–	7,725	–	Post-ACT: 6,286 Post-arthroscopy: 1,043	–	–
NHS reference costs[e]	–	4,469	–	536	815	–	–	–	–	–	–
Genzyme[f]	–	–	–	–	–	6,500	12,649 to 27,587 (mean, 19,231)	–	–	–	–
Verigen[g]	–	–	–	–	–	3,000	–	–	–	–	–
Medical Dynamics[h]	–	–	–	–	–	–	–	–	–	–	2.28
Netten *et al.*, 1999[114 i]	–	–	–	–	–	–	–	16	–	158	–
Base case[j]	52	4,469	146	536	815	6,500 or 3,000	8,167 or 4,667	16	380	158	2.28

FCE, finished consultant episode; ROH, Royal Orthopaedic Hospital (Birmingham)

[a] *This survey of 11 NHS Trusts was performed in conjunction with a forthcoming HTA report on MRI in the diagnosis of knee injury. Mean figures are reported here. The original figures, for 1999, have been inflated using an estimate (4.0%) of the NHS Executive Hospital and Community Health Service (HCHS) Price Index. The latest index figure, for 1998–1999, is 4.03%, which we have also used for 1999–2000*

[b] *These figures were supplied to the West Midlands DES. The original figures, for 1998–1999, have been inflated using the NHS Executive HCHS Price Index. See above footnote[a] for details*

[c] *The original figures were in 1998 US dollars. Costs have been inflated using the medical care sector of the US consumer price index (3.7% for 1999) and converted into pounds sterling at an exchange rate of $1:£0.67, as of January 2000*

[d] *The original figures were in 1998 Swedish krona (SEK). Costs have been inflated by 3% (as suggested by the authors) and converted into pounds sterling at an exchange rate of SEK1:£0.075, as of January 2000*

[e] *NHS reference costs (URL: <http://www.doh.gov.uk/nhsexec/refcosts.htm> accessed 31 May 2000). The latest costs are for 1999 and have been inflated using the NHS Executive HCHS Price Index. See above footnote[a] for details*

[f] *The cost of cell culture was obtained from Genzyme. The figure for surgery was reported by Minas[60] from a survey of 78 facilities performing ACT in the USA. The original figures were in 1997 US dollars. Costs have been inflated using the medical care sector of the US consumer price index (3.4% for 1998 and 3.7% for 1999) and converted into pounds sterling at an exchange rate of $1:£0.67, as of January 2000*

[g] *Figures were supplied to NICE by Verigen Transplantation Service International*

[h] *Medical Dynamics, Chorley, UK: personal communication, 2000. The cost of a CPM device was specified as £2500. To calculate cost per day, we used a conservative estimate of life-span of 3 years*

[i] *Most recent costs are for 1999 and have been inflated using the NHS Executive HCHS Price Index. See above footnote[a] for details*

[j] *Base case is the cost that we believe best reflects likely UK costs and is derived from other costs in the table. ACT cell culture and surgery costs combine the cost of cell culture (based on two possible sources of cells), two arthroscopies (one elective day case and one elective inpatient procedure) and 2 days of hospitalisation as an inpatient. Rehabilitation was estimated to include three outpatient visits, ten sessions of physiotherapy and the availability of a CPM device for use by one patient for 4 weeks*

Appendix 6

Clinical pathway costs

Clinical pathway	Cost (£)			
	Discounted		Not discounted	
Comparator				
Good outcome[a]	852		852	
Poor outcome, no further surgery[b]	1,150		1,168	
Poor outcome, further surgery, good outcome[c]	1,656		1,704	
Poor outcome, further surgery, poor outcome, TKR[d]	5,981		6,289	
ACT	***Carticel***	***Verigen***	***Carticel***	***Verigen***
Good outcome[e]	8,167	4,667	8,167	4,667
Poor outcome, no further surgery[f]	8,465	4,965	8,483	4,983
Poor outcome, further surgery, good outcome[g]	8,971	5,471	9,019	5,519
Poor outcome, further surgery, poor outcome, TKR[h]	13,296	9,796	13,604	10,104

Costs are based upon the following resource use:

[a] *Comparator procedure and rehabilitation*

[b] *Comparator procedure and rehabilitation plus, in year 2, three outpatient visits and ten sessions of physiotherapy*

[c] *Comparator procedure and rehabilitation plus, in year 2, arthroscopy with three outpatient visits and ten sessions of physiotherapy*

[d] *Comparator procedure and rehabilitation plus, in year 2, arthroscopy with three outpatient visits and ten sessions of physiotherapy, plus TKR with one outpatient visit and four sessions of physiotherapy (additional rehabilitation occurs outside the 2-year time frame)*

[e] *ACT procedure and rehabilitation*

[f] *ACT procedure and rehabilitation plus, in year 2, three outpatient visits and ten sessions of physiotherapy*

[g] *ACT procedure and rehabilitation plus, in year 2, arthroscopy with three outpatient visits and ten sessions of physiotherapy*

[h] *ACT procedure and rehabilitation plus, in year 2, arthroscopy with three outpatient visits and ten sessions of physiotherapy, plus TKR with one outpatient visit and four sessions of physiotherapy (additional rehabilitation occurs outside the 2-year time frame)*

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