NICE National Institute for Health and Care Excellence

The use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints

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1 Guidance

This guidance replaces 'Autologous cartilage transplantation for full thickness cartilage defects in knee joints' (NICE Technology Appraisal Guidance 16) issued in December 2000.

For details, see 'About this guidance'.

1.1 Autologous chondrocyte implantation (ACI) is not recommended for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up. Patients should be fully informed of the uncertainties about the long-term effectiveness and the potential adverse effects of this procedure.

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2 Clinical need and practice

2.1 Articular (hyaline) cartilage, which is composed mainly of water and a collagenous extracellular matrix, provides a smooth and resilient surface at the ends of bones, allowing virtually frictionless movement within the knee joint. It also acts as a shock absorber, cushioning the bone from forces of more than five times the body's weight. The cellular component of hyaline cartilage is the chondrocyte, which is responsible for the production and maintenance of the matrix. Cartilage lacks blood and nerve supplies, and it has a limited potential for self-repair.

2.2 Cartilage damage in the knee can be caused directly by injury, often as a result of sporting activity, or spontaneously (a condition called osteochondritis dissecans). Softening of the kneecap cartilage (a condition called chondromalacia patellae) may be caused by trauma, overuse, parts being out of alignment, or muscle weakness, and most often occurs in young adults. Loss of cartilage alone is referred to as chondral damage, whereas loss of bone and cartilage is known as osteochondral damage. Osteochondral damage occurs more commonly in adolescents; it appears that the plane of weakness in this age group lies in the bone rather than at the junction of the cartilage and the bone. Symptoms associated with the loss of hyaline cartilage include knee pain, knee swelling, knee locking (that is, the knee becomes stuck in one position) and giving way of the knee joint. Ultimately, mechanical damage to the joint surface can lead to osteoarthritis.

2.3 Neither the prevalence nor the incidence of hyaline cartilage damage in knee joints is definitively known. Cartilage defects arise from direct injuries or indirectly, appearing immediately or many months or years after the primary insult. It has been estimated that, in the UK, 10,000 patients each year may suffer cartilage damage warranting repair.

2.4 There is no uniform approach to managing hyaline cartilage defects in the knee. There are two main categories of procedures: those intended primarily to achieve symptomatic relief and those that also attempt to re-establish the articular surface. Interventions that aim to re-establish the articular surface include ACI, marrow stimulation techniques (such as abrasion arthroplasty,

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drilling and microfracture) and mosaicplasty (also known as osteochondral transplantation). Other treatment options include knee washout (lavage) with or without debridement.

2.5 The mosaicplasty technique involves removing cylinders of normal cartilage and bone (approximately 4.5 mm diameter) from 'non-weight-bearing' areas of an affected knee and placing them into areas of defective cartilage. Microfracture involves breaching the sub-chondral bone to cause bleeding, and this results in the formation of a blood clot. The clot creates the necessary conditions for a viable population of marrow stem cells to build new tissue within the lesion.

2.6 The impact of treating chondral defects with the interventions described above can be assessed histologically and also by means of a variety of symptom and function rating systems. A histological success is considered to occur when the result includes mainly hyaline cartilage.

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3 The technology

3.1 Autologous chondrocyte implantation (ACI – formerly referred to as autologous cartilage transplantation or ACT) is an approach that has been used to treat defined, symptomatic knee cartilage defects (see Section 2.2). The aim of this treatment is to enable the regeneration of hyaline or hyaline-like cartilage, thereby restoring normal joint function. ACI is not used where there is joint instability that cannot be corrected simultaneously or where there is existing osteoarthritis.

3.2 ACI comprises a series of procedures. First, chondrocytes are harvested arthroscopically from the edge of the affected knee joint. The cells are cultured for a few weeks to expand the cell population (by a factor of about 50). Then, in a second surgical procedure, the cultured chondrocytes are implanted into areas denuded of cartilage by disease or injury. Each damaged area is carefully debrided and covered with a periosteal tissue flap or a porcine collagen membrane, beneath which the autologous cells are injected. In a modification of the treatment, extracted autologous chondrocytes are cultured within a collagen matrix, which is then implanted (matrix-guided ACI). It has been argued that matrix-guided ACI has a number of advantages including allowing the second surgical procedure to be performed by a limited approach or by arthroscopic implantation.

3.3 Recorded adverse effects associated with ACI include joint locking, infections, extension deficit and periosteal hypertrophy where a periosteal cover is used.

3.4 The use of ACI requires special training. Four commercial agencies (Genzyme Ltd UK and Ireland, BBraun/TeTec AG, Geistlich Biomaterials and Verigen UK Ltd) provide services to support ACI in the UK. The actual cost of these services may vary according to the number of procedures performed. In addition to cell culturing, the cost includes shipping and the training of appropriate hospital staff. In-house methods for chondrocyte culture have been developed and are in use at The Robert Jones and Agnes Hunt Orthopaedic & District NHS Trust (RJAH) in Oswestry.

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3.5 Taking note that the acquisition cost may vary according to local agreements, the prices of the ACI services provided by the commercial agencies above are as follows:

- Genzyme Ltd UK and Ireland – £4000 to £5000
- BBraun/TeTec AG – £4000
- Verigen UK Ltd – £3200
- Geistlich Biomaterials – £3500.

The RJAH indicated that the cost of its in-house cell culture service was around £2000 per patient.

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4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group identified five published randomised/quasi-randomised controlled trials. Two trials compared ACI with mosaicplasty and two with microfracture. The final trial compared two different variants of ACI and hence was not discussed further by the Assessment Group. The Assessment Group also sought data on long-term outcomes from case series studies for ACI, for other treatments and for the natural history of the condition. When the original guidance was produced (December 2000), data from completed randomised controlled clinical trials were not available.

Controlled trial evidence – ACI compared with mosaicplasty

4.1.2 In one study (n = 40) all patients treated with ACI had the cartilage defect covered with a periosteal flap. Eleven of the 40 patients (28%) had previously undergone surgery. Treatment was allocated alternately rather than randomly (an allocation procedure subject to bias). It was found that patients recruited to the ACI group (n = 20) scored statistically significantly lower (poorer) on a scale that measures symptoms and function (Lysholm score) than patients allocated to mosaicplasty. A re-analysis of the Lysholm scores from this study, however, found no difference between the two groups if mean change in score was examined rather than absolute score at the end of the study (the preoperative Lysholm score was lower for ACI). There was no statistically significant difference between the treatments when assessed by the other two scoring methods (the Meyers and Tegner scales).

4.1.3 Eight biopsies were taken from six patients in the ACI group and five biopsies were taken in the mosaicplasty group. No details were reported of how patients were selected for biopsy. In the ACI group, the regenerated tissue consisted mostly of fibrocartilage, although localised areas of hyaline-like cartilage could be detected in deeper layers. In the mosaicplasty group a gap remained at the

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site of the transplantation in all five specimens, and analysis found no histological differences between the osteochondral transplants and the surrounding original cartilage.

4.1.4 It was reported that 60% of both groups developed complications within 24 months after surgery. Seven patients in each treatment group had complications that required further surgery. These included: occasional locking of the joint and adhesions; partial rupture of the anterior cruciate ligament; postoperative haemarthrosis; and extension deficit. Five patients in each treatment group had complications that did not require further surgery. One patient, who reported as having no complications after ACI, had an arthroscopy 24 months after ACI to check for meniscopathy.

4.1.5 In the second trial (n = 100), consecutive patients were randomised to have mosaicplasty or ACI, although no details were provided of the allocation methods used. Fifty-eight patients were recruited into the ACI group but only 42 were recruited into the comparator arm. While the majority of the ACI-treated patients had the defect sealed with a porcine collagen membrane, for six patients a periosteal cover was used. All but six patients had undergone previous surgical interventions (excluding arthroscopy). The mean number of previous operations was 1.5 (0–4).

4.1.6 The trial found a greater improvement in a measure of knee function and symptoms (the modified Cincinnati rating system) in the ACI group compared with the mosaicplasty group at 1 year. This difference was statistically significant ($p = 0.002$ calculated by the Committee using a Chi-square test for trend). The number of patients treated with ACI whose cartilage function was rated as excellent or good on the Cincinnati score was 51/58 (88%). This compared with 29/42 (69%) patients following mosaicplasty. Of the 19 patients who underwent biopsy following ACI at 1 year, seven were found to have normal hyaline cartilage, seven mixed hyaline and fibrocartilage, and five fibrocartilage, albeit well-bonded to bone. One of the ACI grafts that showed mixed hyaline and fibrocartilage at 1 year had hyaline cartilage alone at the 2-year biopsy. It was not clear how patients were selected for repeat arthroscopy. The number of patients having biopsy after mosaicplasty was not stated and results were only reported for seven patients whose functional

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outcome was rated as poor. Complications were reported but not by treatment group.

Controlled trial evidence – ACI compared with microfracture

4.1.7 In one trial (n = 80) the defect was sealed with a periosteal flap. Most patients (94%) had previously had knee surgery. Eligible patients were randomised into the two groups during arthroscopy using sealed envelopes (40 patients per group). The study found that for both types of intervention there was a statistically significant improvement in Lysholm scores and a statistically significant reduction in pain from baseline. There was no statistically significant difference between treatments when assessed at 1 or 2 years. After 2 years, 78% of patients who had had ACI experienced less pain compared with 75% after microfracture. Microfracture, however, resulted in improved scores on the physical component of the Short Form-36 (SF-36) compared with ACI at 2 years ($p < 0.005$) but patients who were randomised to the microfracture group had lower scores at baseline. After adjusting for preoperative scores (method not given), microfracture still resulted in statistically significantly improved SF-36 physical component scores compared with ACI.

4.1.8 A 'second-look' arthroscopy was undertaken 2 years after surgery in 32 patients treated with ACI and 35 treated with microfracture. No difference was found between ACI and microfracture as assessed by mean scores on the International Cartilage Repair Society (ICRS) macroscopic evaluation. Following biopsy there was no statistically significant difference between ACI and microfracture with regard to the frequency with which hyaline and fibrocartilage repair tissue were found, but the number of specimens may not have been sufficiently large to detect a statistically significant difference.

4.1.9 There were few patients for whom treatment was considered to have failed (ACI: 2/40 [5%] at 6 and 18 months compared with microfracture: 1/40 [3%] at 15 months). All patients for whom treatment was considered to have failed underwent another cartilage treatment. Arthroscopic debridement was performed in ten (25%) ACI-treated and four (10%) microfracture-treated patients. In ACI-treated patients, shaving was done mainly because of symptomatic tissue hypertrophy. Among microfracture-treated patients, one

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patient underwent manipulation and operative release, and three patients underwent minor debridement.

4.1.10 In the second trial of ACI and microfracture (n = 66; 41 ACI, 25 microfracture), extracted autologous chondrocytes were cultured within a collagen matrix, which was then used for implantation (matrix-guided ACI). It was not reported whether patients had undergone previous surgery. Patients were allocated into the two treatment groups by means of block randomisation methods. The published results from this study reported outcomes for only 19 patients at 1 year and five patients at 2 years.

4.1.11 Although the published version of this study reported that improvements (as assessed by a variety of rating scores) at 1 year were greater in the ACI group versus the microfracture group, no significance levels were reported. The ICRS classification of the defect was found to have improved in both groups, but with no statistically significant differences between them. The abstract of the same study, published with updated data, indicated that results were now available for a period of at least 2 years in 19 patients (10 ACI; 9 microfracture) and for a period of 1 year in 45 patients (27 ACI; 18 microfracture). There were statistically significant differences in two of the three knee-specific rating scores used (Lysholm and Meyers) at 2 years; however, no statistically significant difference was found in ICRS score.

Subgroup analyses

4.1.12 In two of the trials discussed above (one comparing ACI with mosaicplasty and one comparing ACI with microfracture), a number of subgroup analyses were undertaken but these were not defined a priori. They should be viewed therefore with appropriate caution. Briefly, these analyses related to defect size and location, age and other factors. Notably, it is suggested that the relative advantage of microfracture over ACI in the larger ACI–microfracture trial may exist only for small lesions.

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Long-term outcomes

4.1.13 The Assessment Group examined observational studies for longer-term outcomes after ACI, microfracture and mosaicplasty. It also sought to assess the long-term impact of leaving chondral defects untreated.

4.1.14 Three accounts of a Swedish longer-term case series for ACI were identified describing outcomes for up to 11 years after surgery. Participant numbers ranged from 58 to 101, and ACI was performed for moderate to large full-thickness chondral defects of the knee or for osteochondritis dissecans. Good or excellent results were observed in between 82% and 92% of patients.

4.1.15 One account, which included 101 ACI-treated patients with a follow-up of 2–9 years, reported a total of 52 adverse events. These included: superficial wound infections; postoperative fever; postoperative haematomas; intra-articular adhesions; periosteal hypertrophy; and graft failure. The two later accounts, one with 5–11 years' follow-up (n = 61) and another with 2–10 years' follow-up (n = 58), reported that graft failures occurred in 16% and 3% of patients, respectively.

4.1.16 Evidence from natural history studies suggests that sometimes outcomes can be satisfactory in the absence of any directed surgical treatment. One study examined the natural progression of isolated osteochondral defects in the femoral condyle in 15 knees (12 patients) over an average of 109 months (minimum follow-up 4 years). Patients were aged 9–49 years and follow-up was 54–282 months. Lysholm scoring and magnetic resonance imaging (MRI) scans were used to assess the patients. At follow-up, children (younger than age 18 years) had a higher Lysholm score compared with adults (77.1 for children versus 49.9 for adults), although the Mann-Whitney test was inconclusive. MRI scans showed that the lesion had healed in six of seven knees of children, but it had healed in only two of eight knees of adults, with the remaining six knees showing signs of osteoarthritis.

4.1.17 Similar findings were also reported for other natural history studies discussed in the Assessment Report. However, in one study involving 28 young athletes with chondral damage, loss of joint space (suggesting developing osteoarthritis) was observed at follow-up (14 years) in 16 patients. This was

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despite 22 patients having 'good' to 'excellent' function at follow-up. In addition, the Assessment Group noted that the originally unaffected knees showed less early osteoarthritis compared with the knees with the known lesions, but 10 out of 28 knees showed radiographic evidence of osteoarthritis.

Clinical-effectiveness summary

4.1.18 In summary, these trials provide inconsistent evidence of the clinical effectiveness of ACI. The studies were heterogeneous in terms of the patients recruited, the ACI technique used and the measures used to assess outcome. In addition, comparative trial follow-up was limited to 1–2 years. The longer-term case series showed similar benefits under most modes of treatment. There is no trial comparing ACI (or any of the other interventions in the studies described above) with conservative management.

4.2 Cost effectiveness

4.2.1 The literature search undertaken by the Assessment Group identified a number of published economic studies of ACI, although the available data appeared limited. In addition, Verigen UK Ltd submitted unpublished cost-effectiveness data in confidence. The Assessment Group undertook some illustrative modelling, comparing ACI with mosaicplasty and microfracture for patients previously treated with lavage and debridement.

4.2.2 The Assessment Group identified a case series study of 57 patients, which compared the 10-year costs before and after ACI. It also identified a modelling evaluation, which aimed to assess the cost effectiveness of ACI relative to mosaicplasty and microfracture, the outcome being years free of knee replacement. However, neither study reported outcomes as incremental cost per quality-adjusted life years (QALYs) and both were undertaken in a non-UK context.

4.2.3 A US case series study assessed 44 ACI patients preoperatively, and at 12 and 24 months follow-up. The SF-36 was used to assess health-related quality of life. Five of the eight SF-36 dimensions showed statistically significant improvements. In the original paper, these results were converted to

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a QALY gain but the method used was not stated. The quality of life increment from ACI amounted to 0.11 and it was assumed that this gain would be maintained for 40 years. However, the study did not compare ACI with other management strategies.

Modelling by the Assessment Group

4.2.4 The Assessment Group undertook some illustrative modelling of the cost effectiveness of ACI. All the modelling was deterministic. The Group argued that there was insufficient evidence to produce a robust cost per QALY estimate for ACI.

4.2.5 The Assessment Group therefore provided some modelling of the cost effectiveness of ACI in three increasingly speculative stages:

- short term: the application of health-related quality of life improvements at 2 years, coupled with the immediate treatment costs, and a projection forward to 10 years of these quality of life gains
- medium term: as for the above, but modified by the 10-year success rates reported in the case series
- long term: modelling of the long-term effectiveness of treatment with an assumption that only hyaline cartilage development prevents osteoarthritis and prevents the need to offer total knee replacements to some or all patients.

4.2.6 The starting point for all the modelling was patients who had received a diagnosis and initial wash out and debridement. Because these initial costs were common to all patients, they were not included within the modelling. Treatment costs were obtained from Aberdeen Royal Infirmary and Southampton General Hospital; these included the costs of surgery, days as an in-patient, and follow-up physiotherapy. The costs of cell culture in ACI were taken from the Verigen UK Ltd submission. The costs of complications were not included in the modelling.

4.2.7 In the case of the short-term modelling, the Assessment Group applied a health-related quality of life increment of 0.1 for all treatments based on the original 2001 Health Technology Assessment (HTA) monograph on autologous

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cartilage transplantation. In this instance, the analysis was simply one of cost minimisation. Because microfracture was the least costly treatment, it dominated all the others.

4.2.8 For the medium-term modelling, the success rates of 85%, 80% and 88% for ACI, microfracture and mosaicplasty, respectively, were applied to patients over a 10-year period, with only those judged to be successes receiving the quality of life gains. The modelling did not adjust the data to take into account the possibility that there could be different times to the best result and earlier declines (if there are declines) with some treatments compared with others.

4.2.9 As in the short-term modelling, if a common health-related quality of life increment (0.1) results from all treatments, the slightly higher success rate with ACI over microfracture would not be sufficient to justify the additional cost within a 10-year time horizon. However, under these assumptions, mosaicplasty dominates ACI.

4.2.10 In the long-term model, the Assessment Group explored the cost effectiveness of ACI versus mosaicplasty and microfracture over a 50-year time horizon. This model took into account avoidance of knee replacements as well as gains in health-related quality of life. In the base-case analysis it was assumed that only a repair consisting of complete or near-complete hyaline cartilage would prevent the onset of osteoarthritis and the need for a total knee replacement. The analysis implied that the full ACI procedure would be undertaken arthroscopically. The data presented below is based on a discount rate of 1.5% for health benefits and 6% for costs.

4.2.11 Microfracture compared with debridement alone was found to be extremely cost effective, mainly because of the apparent ineffectiveness of debridement. Mosaicplasty was dominated by the less costly option of microfracture.

4.2.12 The incremental cost-effectiveness ratio (ICER) of moving from debridement to microfracture was £1060 per QALY, assuming that all those offered a knee replacement accepted, and £1340 per QALY if only half accepted a total knee replacement. The ICER of ACI versus microfracture was estimated to be £3200 per QALY, assuming that all those offered a knee replacement

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accepted, and £3650 per QALY if only half accepted a total knee replacement. Mosaicplasty was dominated in both scenarios.

4.2.13 The Assessment Group undertook a number of separate sensitivity analyses on the long-term model. One such analysis examined the impact of applying the success rates and biopsy data from the larger of the two studies comparing ACI and microfracture described above. The cost effectiveness of ACI relative to microfracture worsened under this scenario.

Cost-effectiveness summary

4.2.14 As noted above, the data on the relative effectiveness of ACI compared with microfracture and the still relatively experimental mosaicplasty technique are inconsistent. Furthermore, there is a lack of long-term follow-up, and the quality of life gain from treating with ACI compared with other alternatives remains unclear.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of ACI, having considered evidence on the nature of the condition and the value placed on the benefits of ACI by people who have undergone the procedure, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee carefully considered new evidence from controlled trials that has become available since the publication of the original guidance. It was not, however, persuaded that the new data establish the effectiveness of the technology.

4.3.3 The Committee noted that the cost-effectiveness information, including the modelling undertaken by the Assessment Group, was highly speculative because of the limited data available, particularly in view of the lack of long-term data. Consequently, the Committee agreed that any conclusions about

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the relative cost effectiveness of ACI versus treatment alternatives still require better effectiveness data than are currently available.

4.3.4 The Committee noted that the trial data provided inconsistent evidence of the benefits of ACI and the trials had a follow-up of only 1 to 2 years in a condition where long-term outcomes are critical. There is no evidence currently available that allows a determination of the absolute benefit of ACI (or indeed of microfracture or mosaicplasty) over conservative treatment. The Committee further noted the trial histological evidence. The findings on the quality of the cartilage produced – and the influence of this cartilage on functional outcomes in the medium to long term – were unclear. Health-related quality of life data on patients who undergo ACI and other procedures, including knee replacement, were also considered inadequate.

4.3.5 The Committee agreed that because the clinical effectiveness of ACI is uncertain, it should only be performed within the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life. This would normally be by randomised controlled trials, although it might sometimes be reasonable to evaluate refractory cases with well-designed observational studies. In addition, the Committee emphasised the importance of collecting long-term data to address whether ACI reduced the need for long-term joint replacement and to assess long-term adverse effects. Consequently, it was of the strong opinion that participants in these clinical studies should be entered into registries for collecting information on long-term outcomes (including adverse effects) for both ACI and comparator interventions.

4.3.6 The Committee also identified the need for better information on patient characteristics (such as lesion size) and treatment protocols; this may be important in determining outcomes after treatment with ACI. The Committee agreed that further trials and long-term follow-up data would be crucial in clarifying whether there are particular benefits for certain patient subgroups.

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5 Recommendations for further research

5.1 As discussed in Section 4, evidence on the benefits of ACI compared with other treatments is lacking. Key issues relate to medium- to long-term outcomes and the durability of different types of chondral repair. ACI and other chondral resurfacing techniques are rapidly evolving and there is a lack of evidence on the relative effectiveness of different approaches.

5.2 Research is currently being undertaken in a variety of areas and includes a number of randomised controlled trials. A Medical Research Council (MRC)-funded randomised trial (ACTIVE) has recently started, which aims to examine the benefits of two forms of ACI (periosteal- and collagen-covered ACI) versus alternative interventions (for example, microfracture and mosaicplasty) in previously treated patients. A second UK-based multi-centre randomised controlled trial is in progress, comparing ACI with matrix-guided ACI. A third ongoing randomised controlled trial is TIGACT 01, comparing ACI with microfracture in the repair of difficult-to-treat cartilage defects of the knee joint. It is planned that this study will provide yearly follow-up over a 5-year period. A fourth ongoing trial is a multi-centre, prospective, longitudinal within-patient evaluation of the effectiveness of periosteal-covered ACI compared with non-ACI surgical treatment for articular cartilage defects of the knee in patients who have previously undergone surgery (the STAR study). This study is being carried out in line with Food and Drug Administration (FDA) regulatory requirements for Genzyme Ltd UK and Ireland's ACI product. The FDA also required Genzyme to undertake a post-marketing registry-based analysis. In addition, a German study is under way evaluating the efficacy of a specific rehabilitation programme following treatment with matrix-guided ACI compared with conventional aftercare.

5.3 Further research is needed to compare chondrocyte implantation techniques, mosaicplasty and microfracture with conservative treatment such as intensive physiotherapy. Further information is also needed on the relationship between histological or radiological outcomes and the avoidance of osteoarthritis and impairments in health-related quality of life. The impact of chondral resurfacing on the need for knee replacement should also be investigated.

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5.4 Research is needed to identify the most appropriate measure of functional outcome following surgical and non-surgical intervention, and to relate this to a generic measure of health-related quality of life.

5.5 Systematic collection of information on long-term outcomes is needed for all patients treated with ACI, for example through the development of national registries.

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6 Implications for the NHS

6.1 The net budget impact on NHS expenditure in England and Wales will depend on the number of patients in, and funding arrangements for, the clinical studies recommended in Section 1.1. The Institute expects there to be some NHS expenditure on this technology.

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7 Implementation and audit

7.1 NHS hospitals and clinicians who care for people who have articular cartilage defects of the knee joint should review their current practice and policies to take account of the guidance set out in Section 1.

7.2 ACI should be performed only within the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data. Patients should be fully informed of the uncertainties about the long-term effectiveness and the potential adverse effects of this procedure.

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8 Related guidance

8.1 This guidance is a review of:

- National Institute for Clinical Excellence (2000) Guidance on the use of autologous cartilage transplantation for full thickness cartilage defects in knee joints. *NICE Technology Appraisal Guidance* No. 16. London: National Institute for Clinical Excellence.

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9 Review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

9.2 The guidance on this technology will be considered for review in May 2008.

Andrew Dillon
Chief Executive
May 2005

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Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The committee is split into three branches. In order to ensure consistency, the chair of each branch is also a member of a branch of which he is not chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Ms Julie Acred
Chief Executive, Derby Hospitals, Southern Derbyshire Acute Hospitals NHS Trust

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley
Vice Chairman, InContact

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Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

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Dr Peter I Clark
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Ms Donna Covey
Chief Executive, National Asthma Campaign

Dr Mike Davies
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Professor Jack Dowie
Health Economist, London School of Hygiene

Professor Gary A Ford (Vice Chair)
Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Dr Fergus Gleeson
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Ms Sally Gooch
Director of Nursing, Mid Essex Hospital Services Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London

Miss Linda Hands
Clinical Reader in Surgery, University of Oxford

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Professor Robert Kerwin
Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Ms Joy Leavesley
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Ms Rachel Lewis
Staff Nurse (Nephrology), Hull Royal Infirmary

Professor Jonathan Michaels
Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne
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Dr Neil Milner
General Medical Practitioner, Sheffield

Dr Rubin Minhas
General Practitioner with a Special Interest in Coronary Heart Disease, Primary Care CHD Lead, Medway PCT & Swale PCT

Mr Richard Devereaux-Phillips
Public Affairs Manager, Medtronic Ltd

Professor Mark Sculpher
Professor of Health Economics, Centre for Health Economics, University of York

Dr Ken Stein
Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)
Professor of Public Health, University of Birmingham

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Mr Miles Scott
Chief Executive, Harrogate Health Care NHS Trust

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Mr Francis Ruiz
Technical Lead, NICE project team

Dr Sarah Cumbers
Project Manager, NICE project team

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Appendix B. Sources of evidence considered by the Committee

A. The Assessment Report for this appraisal was prepared by Health Technology Assessment Group, University of Aberdeen:

Clar C, Cummins E, McIntyre, L, et al. *Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints*. August 2004.

B. The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I) Manufacturer/sponsors:

- BBraun Medical Ltd/TeTec AG
- Geistlich Biomaterials[1]
- Genzyme Ltd UK and Ireland
- Oscell (in-house service of the Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust)
- Verigen UK Ltd

II) Professional/specialist and patient/carer groups:

- Arthritis & Musculoskeletal Alliance (ARMA)
- Arthritis Care
- Arthritis Research Campaign
- Bracknell PCT
- British Association of Day Surgery

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- British Institute of Musculoskeletal Medicine
- British Society for Rheumatology
- Chartered Society for Physiotherapy
- Royal Association for Disability & Rehabilitation
- Royal College of Nursing
- Royal College of Surgeons

III) Commentator organisations (without the right of appeal):

- Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust
- Royal National Orthopaedic Hospital (Stanmore)
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland

C. The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on autologous chondrocyte implantation by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor George Bentley, Professor of Orthopaedics, Royal National Orthopaedic Hospital
- Mr Steve Goldsworthy, patient expert
- Ms Jackie Lane, patient expert
- Susan Brady, patient expert

[1] Geistlich Biomaterials was added to the list of consultees during the ACD consultation phase.

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Changes after publication

March 2014: minor maintenance

March 2012: minor maintenance

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About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance replaces 'Autologous cartilage transplantation for full thickness cartilage defects in knee joints' (NICE Technology Appraisal Guidance 16) issued in December 2000.

The Institute reviews each piece of guidance it issues.

The review and re-appraisal of the use of autologous chondrocyte implantation (ACI) for the treatment of cartilage defects in knee joints has resulted in modifications to the guidance. Specifically:

- the recommendation that ACI should not be used for routine primary treatment has been expanded to include all treatment levels
- the recommendation on the use of ACI in clinical trials has been revised to recommend that all patients receiving ACI should be enrolled in ongoing or new clinical studies
- a recommendation has been made that patients should be fully informed of the uncertainties about the long-term effectiveness and the potential adverse effects of this procedure.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have

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regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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