

# Autologous chondrocyte implantation in the knee: systematic review and economic evaluation

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**Declared competing interests of authors:** Leela C Biant has had institutional research support from Sanofi-aventis (not related to autologous chondrocyte implantation), but has no personal conflict of interest.

Published February 2017

DOI: 10.3310/hta21060

## Scientific summary

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Health Technology Assessment 2017; Vol. 21: No. 6

DOI: 10.3310/hta21060

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# Scientific summary

## Background

The surfaces of the bones in the knee are covered with articular cartilage, a rubber-like substance that is very smooth, allowing frictionless movement in the joint, and acting as a shock absorber. The cells that form the cartilage are called chondrocytes. Natural cartilage is called hyaline cartilage.

Various methods have been used to try to repair cartilage defects, usually aiming to replace the damaged cartilage using bone marrow cells, including stem cells, which then form a tissue called fibrocartilage. The commonest way of doing this is called microfracture (MF). Small holes are drilled through the bone underlying the damaged area to allow the marrow cells to fill the defect. However, the fibrocartilage formed is less durable than natural hyaline cartilage.

Autologous chondrocyte implantation (ACI) aims to replace the damaged cartilage with hyaline cartilage. A small piece of articular cartilage is taken from the knee, and the chondrocytes are cultured in the laboratory, until there are millions of cells, which are implanted into the damaged area.

The methods of ACI have evolved. In the first generation of ACI (ACI-P – ‘P’ for periosteum), the cultured cells were implanted as a liquid suspension, and covered with a cap made from periosteum – the tough fibrous tissue that covers bones. This required a procedure to harvest the periosteum, which caused discomfort to the patient afterwards.

In second-generation ACI, the periosteal cover was replaced by a collagen cover (ACI-C for short), but the cells were still in liquid suspension, and the cover still had to be stitched in place.

One development in ACI has been ‘characterisation’, a process in which the cells thought to have the best ability to form hyaline cartilage are selected during culture.

In the third generation of ACI, the cells are seeded or loaded into a collagen membrane, which is implanted into the defect. This is referred to as matrix-applied chondrocyte implantation (MACI).

## Decision problem

The scope from the National Institute for Health and Care Excellence (NICE) for this appraisal mentions three forms of ACI:

1. The ChondroCelect system from TiGenix (Leuven, Belgium), in which characterised cells are capped with biodegradable collagen: ACI-C.
2. The Matrix ACI system [matrix-applied characterised autologous cultured chondrocyte implant (MACI®)] now marketed by Vericel (Cambridge, MA, USA).
3. ACI wherein the cells are cultured in hospital or research laboratories, such as the Robert Jones and Agnes Hunt Hospital in Oswestry, termed ‘traditional ACI’ in the NICE scope.

The main comparator is MF.

## Clinical effectiveness

We reviewed previous systematic reviews of the comparative effectiveness of various forms of ACI and MF. We then searched for trials [randomised controlled trials (RCTs)] that used the most recent forms of ACI.

The reviews were mostly inconclusive on the choice between ACI and MF, for reasons including poor quality of primary studies, the heterogeneities of patients recruited, ACI methods used, outcome measures, variations in previous surgery and short follow-up periods.

Four RCTs have been published since the last appraisal provided evidence on the efficacy of ACI. These are:

Basad E, Ishaque B, Bachmann G, Stürz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. *Knee Surg Sports Traumatol Arthrosc* 2010;**18**:519–27. <http://dx.doi.org/10.1007/s00167-009-1028-1>.

SUMMIT (Superiority of Matrix-induced autologous chondrocyte implant versus Microfracture for Treatment of symptomatic articular cartilage defects) Saris D, Price A, Widuchowski W, Bertrand-Marchand M, Caron J, Drogset JO, *et al.* Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. *Am J Sports Med* 2014;**42**:1384–94. <http://dx.doi.org/10.1177/0363546514528093>.

The TIG/ACT/01/2000 trial (hereafter TIG/ACT trial) Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP, TIG/ACT/01/2000&EXT Study Group. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. *Am J Sports Med* 2011;**39**:2566–74. <http://dx.doi.org/10.1177/0363546511422220>.

The ACTIVE (Autologous Chondrocyte Transplantation/Implantation Versus Existing Treatment) trial (390 patients) [Keele University. *ACTIVE Trial Web Site*. 2011. URL: [www.active-trial.org.uk/](http://www.active-trial.org.uk/) (accessed 25 July 2016)].

Two of the trials, Basad *et al.* with 60 patients and SUMMIT by Saris *et al.* with 144 patients, compared MACI with MF. The TIG/ACT trial with 118 patients compared ACI-P with characterised chondrocytes against MF. The ACTIVE trial compared several forms of ACI against standard treatment, mainly MF.

The primary outcome measures in the Basad trial were Tegner and Lysholm scores. Lysholm scores improved in both MACI and MF groups from baseline to 12 months, but the improvement was maintained to 24 months only in the MACI group (92 vs. 69;  $p = 0.005$ ). Tegner scores improved in both groups, but more so in the MACI group.

In the SUMMIT trial, improvements in knee injury and osteoarthritis outcome knee injury and osteoarthritis outcome scores (KOOSs) were significantly greater in the MACI group than in the MF group. The proportion of responders was higher with MACI. Factors that predicted better results with MACI were male gender, a median age of < 34.5 years, presence of a single lesion due to acute trauma, history of only one previous surgical procedure, and lesion of size > 4 cm<sup>2</sup> located on the femoral condyle. More patients in the MF group reported adverse events (AEs), most frequently arthralgia.

In the TIG/ACT trial of ChondroCelect, the overall KOOS improved at 60 months with both treatments, with no statistically significant difference. Patients with onset of symptoms < 3 years' duration did better with ACI-P. More patients in the ACI-P group experienced AEs but they were mild to moderate in intensity.

The ACTIVE trial is comparing ACI (including ACI-P, ACI-C and MACI) against standard treatments (MF, abrasion, drilling, mosaicplasty).

Autologous chondrocyte implantation is less successful in patients who have had previous MF than if it is done as first repair, because MF damages the subchondral bone.

## Longer-term results: survival analysis

The trials included under the original scope from NICE on second- and third-generation ACI provided results only up to 3 and 5 years, and, for modelling of cost-effectiveness, longer-term outcome data were desirable. It was decided that longer-term data from ACI-P could be used, based on an assumption that data on longer-term outcomes of chondral defect repairs from studies of ACI-P could be extrapolated to survival of repairs after ACI-C and MACI. ACI-P has been superseded because the new techniques are simpler and quicker, and because the use of periosteum required harvesting and ensuring a watertight cap, and could lead to overgrowth hypertrophy requiring reoperation and shaving of the graft, and the extra discomfort to patients from these procedures. The collagen cap is much easier to use. The third generation of ACI in which the cells are seeded onto the collagen membrane is quicker still.

It was felt that results after ACI-C and MACI would at least be no worse than after ACI-P.

We searched for studies reporting longer-term results of ACI and MF.

Survival analysis – time to failure in longer-term studies: we included six studies of long-term results of ACI, the best of which was by Nawaz *et al.* from Stanmore. (Nawaz SZ, Bentley G, Briggs TW, Carrington RW, Skinner JA, Gallagher KR, Dhinsa BS. Autologous chondrocyte implantation in the knee: mid-term to long-term results. *J Bone Joint Surg Am* 2014;**96**:824–30.) It was best because of its size (827 patients – greater than the other studies put together); because it reflected UK practice (albeit from a centre of excellence); because it provided data from the period 1998–2008, on different generations of ACI; and because it provided very useful subgroup data.

The findings of the Nawaz study include:

- ACI graft survival was 78% at 5 years and 51% at 10 years for the whole cohort.
- There was no difference between survival rates of ACI-P and ACI-C, and MACI. Most (63%) received MACI.
- Outcomes were much poorer in patients who had had previous attempts at cartilage repair such as MF, with an almost fivefold failure rate.
- The presence of osteoarthritis (OA) increased failure rates. Patients with Kellgren–Lawrence grades 2 and 3 had only 25% graft survival to 10 years.

We used the Nawaz results as the main input into survival analysis and cost-effectiveness, but also did a sensitivity analysis (SA) incorporating five other long-term studies of ACI.

There were few long-term studies of MF. We constructed survival curves based on 5-year data from only three studies: two trials with 40 and 61 patients and an observational study from routine care in the USA with 3498 patients having MF.

The ACI groups had lower failure rates than the MF cohorts, except for the ACI group with previous attempts at repair or with OA. Data were sparse on results of MF in previously treated patients.

In summary:

- More long-term evidence was available for ACI than for MF.
- Study data were generally still too short term. Only one published study allowed an estimate of observed median time to failure.
- Caveat: immaturity of failure data necessitated parametric modelling beyond observed data so as to predict lifetime failure. Such extrapolations assume that curves based on the observed data will continue.

- Most participants in most studies had had previous attempts at repair. Two ACI studies with survival analyses extending to at least 10 years reported that treatment failure was far more frequent in patients who had experienced prior intervention(s). This reduced the likelihood of success after ACI and makes extrapolation of results from older studies to ACI as first procedure rather pessimistic.
- The best fits of long-term failure after ACI were usually characterised by models that, when extrapolated beyond the observed data, indicated gradually decreasing hazard (probability of failure decreasing with time).
- Conversely, good fits to limited data available for MF were characterised by models that indicated linearly increasing hazard (probability of failure increasing with time).

## Cost-effectiveness

### Review of previous economic studies

We reviewed existing economic evaluations of the use of ACI and MF for repairing symptomatic articular cartilage defects of the knee. A broad search was done in MEDLINE, EMBASE, NHS Economic Evaluation Database and Web of Science for studies published since the last Health Technology Assessment review in 2005.

We found six relevant articles, all with shortcomings, most notably the lack of long-term clinical follow-up and good quality-of-life (QoL) data.

### Review of submissions received

We reviewed the submissions from Swedish Orphan Biovitrum AB (SoBi, Stockholm, Sweden) on ChondroCelect, from Aastrom Biosciences (now Vericel, Cambridge, MA, USA) on MACI®, and from OsCell, including unpublished data from the ACTIVE trial.

Swedish Orphan Biovitrum AB developed a de novo Markov economic model. Their modelling assumed that MF was the comparator; if the first repair fails then patients can have a second repair, but only with MF, and the main driver was time to failure of the first repair. They used data from the TIG/ACT trial. Their key assumptions were that fewer patients who had ACI needed second repairs and that they had a longer duration of success, thereby postponing the need for knee replacement. Their base-case incremental cost-effectiveness ratio (ICER) was about £9000 per quality-adjusted life-year (QALY).

Aastrom Biosciences did not provide any cost-effectiveness analysis but did provide a costing forecast. They explored two scenarios, one with MACI or ACI as first procedure, and the other with MF. Based on data from the SUMMIT trial, they estimated that there would be cost savings from using MACI due to the lower need for further repairs.

The Oswestry group provided a cost-effectiveness analysis for the ACTIVE trial. This analysis used EQ-5D-3L (EuroQol-5 Dimensions, three-level version) data based on up to 8 years of follow-up. It assumed a cost for cells of £4125, based on production by OsCell. The data showed little difference between ACI and MF for the first 4 years but, after that, EQ-5D results were better in the ACI group, with a cost per QALY for ACI compared with MF of around £6000.

### Warwick Evidence modelling

We constructed a lifetime Markov model, starting with a cohort of people aged 33 years with symptomatic articular cartilage defects of the knee treated with ACI or MF. The analysis considered the need for subsequent events including further repairs and later knee replacements. Most patients (87.5%) did not need a second repair. We created two scenarios to allow direct comparisons: in scenario 1 all second repairs were ACI, and in scenario 2 all second repairs were MF. Secondary analyses considered other options including ACI after prior MF.

For the base-case analysis, we used data mainly from the TIG/ACT trial of ChondroCelect and the SUMMIT trial of MACI.

The results indicated that ACI is more cost-effective than MF as a first repair, and that if a second repair is needed this should also be ACI. The base-case discounted ICER for ACI compared with MF was just over £14,000 per QALY for scenario 1, and just under £16,000 per QALY for scenario 2.

Results from SAs were in line with the base-case results.

The key drivers in the base case were the cost of cells for ACI and the relative durations of benefit from ACI and MF. After the first few years (varying among studies) ACI was more beneficial (more gain in QALYs) and led to cost savings to the NHS [fewer people in need of a second repair or of a total knee replacement (TKR), and first TKR postponed reducing the need for second TKR].

Limitations in the economic analyses included uncertainties with long-term progression rates and QoL data.

We then used data from the long-term survival analysis, using the whole Nawaz cohort results for ACI, and pooling the MF results from three studies. At the request of NICE, we used an implantation cost of £2396 (assuming an inpatient stay), and we omitted the option for MF failure to be followed by another MF. So the options were:

- MF followed by ACI if another procedure was considered necessary in the short term. In the long term, patients would be considered for knee replacement, but most would still be too young for that after MF failure.
- ACI followed by MF if another attempt at repair was necessary.
- ACI followed by a second ACI if another attempt at repair was necessary.

Microfracture followed if necessary by ACI was the lowest cost option, and we compared other options with that. ACI followed by MF was dominated by ACI followed if necessary by ACI, because of the poor long-term results of MF.

The ICER for ACI as primary procedure compared with MF was around £19,000 – a little less in deterministic analysis, a bit more in probabilistic. A caveat is necessary – the marginal QALY gains were very small, at 0.0650 in deterministic and 0.0824 in probabilistic.

We carried out a range of SAs. In the base case, we used a cell cost of £16,000 in line with published prices, but we are aware of discounted prices that vary by time and place. The deterministic ICERs for ACI as first procedure compared with MF were as follows:

- cost of cells £6000 – ICER £7414
- cost of cells £8000 – ICER £9700
- cost of cells £12,000 – ICER £14,272.

We tested a series of utility assumptions for those whose first repair was not successful but who decided not to have another. In our first analysis, we assumed that they had had some benefit, and had improved from a utility of 0.654 before the repair to 0.691 afterwards. NICE asked us to assess the effect of the following assumptions for utilities:

- Utility set to the same as failure (0.654) – ICER £15,634.
- Utility after failure set to same as success (0.817) – ICER £62,658. This assumption greatly increases utility gain among those who do not get good results after MF, and reduces the marginal QALY gains from ACI.
- Utility set to midpoint of success and failure (0.746) – ICER £27,123. This also reduces the marginal QALY gains from ACI as first procedure, because the larger proportion that does not do well after MF has their utility increased.

The Nawaz study provides very useful data on subgroups:

- Previous attempts at repair, such as MF – ICER £38,262. ACI is much less successful if the underlying bone has been damaged.
- Individuals without prior repair attempts – ICER £15,659.
- Kellgren–Lawrence grade 0 – no radiological sign of OA – ICER £15,618.
- Kellgren–Lawrence grade 1 – radiological signs of early OA – ICER £17,104.
- Kellgren–Lawrence grade 2 – ICER £20,096.
- Kellgren–Lawrence grade 3 – ICER £21,207.

In a SA, instead of relying on the Nawaz data alone, we tested the effect of pooling six ACI studies and found an ICER of £16,708.

Vericel provided details from an unpublished study in which patients with chondral defects were reported to have a baseline utility of 0.484. Using that baseline and their 3-year utility gain would give an ICER of £15,648. The baseline utility looks surprisingly low.

## Strengths and limitations in evidence

We now have longer follow-up than was available for previous appraisals, and data from several new trials. The ACTIVE trial has data on some patients to 8 years and will eventually have 10 years of follow-up for all. The TIG/ACT trial has 5 years of follow-up. However, the two trials of MACI against MF had only 2 years of follow-up. There are few long-term MF studies.

## Research needs

Autologous chondrocyte implantation is less successful among people with OA, but ICERs can be in the range usually considered acceptable. ACI may have a place in early OA with focal damage – research is needed in this group.

## Conclusions

Caveats are necessary. There were more long-term studies of ACI than of MF. Using longer-term data than were available in the trials, MF comes out much less well. However, there are few long-term studies of MF, and extrapolation beyond observed data is subject to uncertainties. The evidence base is much stronger for ACI, but in older studies most patients had had previous attempts at repair. ACI is less successful after previous attempts at repair. Previous studies may therefore provide a pessimistic assessment. Most, but not all, studies suggest that ACI is more effective if used soon after the cartilage injury. A key conclusion is that ACI will give better results if used as first repair procedure.

In summary, the evidence base for ACI has improved since the last appraisal by NICE. In most analyses, the ICERs for ACI compared with MF appear to be within a range usually considered acceptable.

## Study registration

This study is registered as PROSPERO CRD42014013083.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.



ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

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## This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 13/65/01. The protocol was agreed in May 2014. The assessment report began editorial review in January 2015 and was accepted for publication in June 2016. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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