

# Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee

Technology appraisal guidance

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This guidance replaces TA89.

# 1 Recommendations

1.1 Autologous chondrocyte implantation (ACI) is recommended as an option for treating symptomatic articular cartilage defects of the knee, only if:

- the person has not had previous surgery to repair articular cartilage defects
- there is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis)
- the defect is over 2 cm<sup>2</sup> and
- the procedure is done at a tertiary referral centre.

## Why the committee made these recommendations

Clinical trial evidence shows that ACI can improve the symptoms of articular cartilage defects of the knee. There is evidence that it is likely to be more successful in people who haven't had any previous knee repair surgery, and in people who have very little osteoarthritic damage in the knee. But, it is unclear how well ACI works in the long term compared with microfracture, the most commonly used alternative treatment.

The consensus among UK clinicians is that ACI is the only effective treatment option for defects that are over 2 cm<sup>2</sup> when symptoms persist after non-surgical management.

The most accurate cost-effectiveness estimate for ACI compared with microfracture is uncertain, and is not likely to be under £20,000 per quality-adjusted life year (QALY) gained for everyone who is eligible to have ACI. But the cost-effectiveness estimate is lower in people in whom ACI has a better chance of success. This includes people who haven't had any previous knee repair surgery, and people who have very little osteoarthritic damage in the knee. In these people, the most accurate cost-effectiveness estimate is likely to be under £20,000 per QALY gained.

## 2 The technologies

Autologous chondrocyte implantation (ACI)	
Marketing authorisations	<p>The OsCell John Charnley Laboratory has approval from the Medicines and Healthcare products Regulatory Agency to provide <b>traditional ACI services</b> under a hospital exemption from the advanced therapy medicinal products regulation for products prepared on a non-routine basis. It also has approval from the Human Tissues Authority for procuring, testing, storing and importing human tissues and cells for human application, and storing relevant material that has come from a human body for use for a scheduled purpose. The indication for use of traditional ACI in the knee is for the repair of single or multiple symptomatic, full-thickness cartilage defects of the joint with or without bone involvement in adults. Traditional ACI involves implanting a cell suspension under either a periosteal- or collagen-based membrane. Traditional ACI can be considered when the Oswestry Risk of Knee Arthroplasty (ORKA) score is 3 or 4, but only when other factors can be corrected, for example, using meniscal allograft or realignment osteotomy.</p> <p><b>Matrix-associated chondrocyte implantation (MACI)</b> had a European marketing authorisation for the repair of symptomatic, full-thickness cartilage defects of the knee (grades III and IV of the Modified Outerbridge Scale) between 3 cm<sup>2</sup> and 20 cm<sup>2</sup>. The marketing authorisation is currently <b>suspended</b> while Vericel validates a new site for culturing cells.</p> <p><b>ChondroCelect</b> had a European marketing authorisation for repair of symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society grades III or IV), which was <b>withdrawn</b> by TiGenix during the course of this appraisal for commercial reasons.</p> <p>ACI is contraindicated in people with severe osteoarthritis of the knee.</p>
Price	<p>Costs may vary in different settings because of negotiated procurement discounts.</p> <p>The recommendations are based on a maximum cell cost of £16,000.</p>

## 3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence from a number of sources. See the [committee papers](#) for full details of the evidence.

### Current treatment

#### ACI is an option after best supportive care but before knee replacement

- 3.1 The committee considered the treatment pathway for treating symptomatic cartilage defects of the knee. It understood that people with articular cartilage defects will first be offered best supportive care. This includes exercise, weight loss, physiotherapy, intra-articular corticosteroid injections, analgesia, off-loading, and applying heat/cold or transcutaneous electrical nerve stimulation. The committee heard from clinical experts that people with articular cartilage defects will be considered for surgery (microfracture, mosaicplasty or autologous chondrocyte implantation [ACI]) only if symptoms persist after best supportive care. It understood that a patient having ACI would have 2 surgical procedures: 1 to harvest chondrocytes from a non-damaged portion of the knee, and another to implant the cells in the damaged area. Between the 2 procedures, the cells would be cultured in a laboratory. The committee heard that the choice between ACI, microfracture and mosaicplasty depends on the size of the defect, previous surgery, age, BMI and the condition of the cartilage. The committee was aware of the published [consensus of 104 UK surgeons](#) with specialist knowledge of surgical repair techniques for articular chondrocyte defects of the knee. It states that microfracture is less effective in articular cartilage defects over 2 cm<sup>2</sup> and that ACI is the surgery of choice for articular cartilage defects over 2 cm<sup>2</sup>. The committee heard that, in current clinical practice, the preferred surgery for defects smaller than this was microfracture. However, because there is variation in access to ACI, microfracture is currently the most common procedure for articular cartilage defects of all sizes. The clinical experts

advised that, for people whose symptoms persist after having ACI or microfracture, other interventions such as mosaicplasty, debridement and lavage, osteotomy, further physiotherapy or a second ACI would be considered. The committee heard that, after microfracture, surgeons are unlikely to offer patients a second microfracture procedure. Total and partial knee replacement are options later in the treatment pathway, if the damage to the cartilage leads to advanced osteoarthritis. The committee heard from the clinical experts that, in clinical practice, total knee replacement is considered to be 'salvage treatment' (particularly in people younger than 55 years) to be used when people have exhausted all other options.

## Comparators

### Microfracture is the most relevant comparator for decision-making

3.2 The final scope issued by NICE listed a number of comparators:

- Microfracture – the committee agreed this was a relevant comparator.
- Mosaicplasty – the committee noted differing views on the use of mosaicplasty in current NHS clinical practice. One clinical expert stated that mosaicplasty was generally used as an alternative to microfracture. However, the committee was persuaded by the assessment group's clinical advice that mosaicplasty is rarely used in NHS clinical practice.
- Osteotomy – the committee heard from a clinical expert that this would mainly be used to treat osteoarthritis of the knee, but may be used together with ACI in some people. The committee agreed that osteotomy was not a relevant comparator.
- Best supportive care – the committee agreed that ACI would only be used when symptoms persist after best supportive care (see [section 3.1](#)), and so concluded that it was not a relevant comparator.

- Total knee replacement – the committee agreed that this would be offered later in the treatment pathway, and would not be considered for people for whom ACI was an option (see section 3.1). As such, the committee concluded that knee replacement was not a relevant comparator.

The committee appreciated that there would be some variation in the use of these procedures in clinical practice because of the clinical experience and preference of the treating clinician and the availability of treatment. However, the committee concluded that microfracture is the most frequently used alternative to ACI in the NHS, and was the most relevant comparator for ACI in this appraisal.

## Marketing authorisations

### **The recommendations only apply to technologies with a current marketing authorisation or an MHRA hospital exemption**

3.3 The committee discussed the technologies listed in the final scope issued by NICE:

- TiGenix, which held the marketing authorisation for ChondroCelect, withdrew its marketing authorisation over the course of the appraisal.
- The European marketing authorisation for matrix-associated chondrocyte implantation (MACI; held by Vericel) was suspended at the time of the appraisal because Vericel had closed its European laboratory for commercial reasons. Vericel told the committee that it was currently discussing accrediting its US laboratory with the European Medicines Agency, with the aim of reactivating its European marketing authorisation.



- OsCell John Charnley Laboratory is affiliated with a tertiary referral NHS orthopaedic hospital. It is permitted by the Medicines and Healthcare products Regulatory Agency (MHRA) to provide its services through the MHRA's hospital exemption from the regulation on advanced therapy medicinal products.

The committee heard from OsCell that, if ACI was more widely available in the NHS, it envisaged that more NHS laboratories would be established specialising in selecting and culturing chondrocytes for ACI. The committee heard from NICE that its technology appraisal guidance only applies to technologies with a current marketing authorisation, but that the MHRA's hospital exemption regulation means that ACI provided by the OsCell John Charnley Laboratory meets this criterion. The committee concluded that it was relevant to consider all the data on clinical and cost effectiveness it had received. However, its recommendations would apply only to technologies with a current marketing authorisation or an MHRA hospital exemption from the regulation on advanced therapy medicinal products.

## Patient experience

### Articular cartilage defects are debilitating and patients would welcome ACI

- 3.4 The committee noted that 29 people had submitted statements to NICE describing their experiences of articular cartilage defects and ACI. It heard that the symptoms of knee cartilage damage include pain, swelling, locking and joint instability, and that these symptoms negatively affect quality of life and a person's ability to do daily activities. In particular, many people with articular cartilage defects of the knee were very active before their injuries, so the physical impairment has had a major effect on their lives. The patients commented that recovery time was long with ACI but that the benefits were worth it. The clinical experts commented that some people prefer microfracture because of its shorter recovery time, whereas some people (such as competitive athletes) prefer ACI because the results are likely to last longer. Several people stated that, after having ACI, they had fewer symptoms and were able to resume daily activities. The committee commented that people who had positive experiences with ACI were more likely to provide comments to

NICE and, as such, the patient statements may not reflect the full range of people's experiences. But, overall, the committee concluded that some patients were satisfied with the outcomes of ACI, and would welcome it as a treatment option.

## Clinical trial evidence

### The evidence for short-term outcomes came from 4 randomised controlled trials

3.5 The committee considered the clinical-effectiveness evidence for ACI in terms of reducing pain and improving functional impairment associated with articular cartilage defects. For the first 2 committee meetings, the assessment group identified 4 randomised controlled trials that were relevant to the final scope issued by NICE:

- Basad et al. (2010), comparing MACI with microfracture in 60 patients over 2 years.
- SUMMIT, comparing MACI with microfracture in 144 patients over 5 years.
- TIG/ACT, comparing ACI using characterised chondrocytes (ChondroCelect) with microfracture in 118 patients over 5 years.
- ACTIVE, comparing several forms of ACI with standard treatment (such as microfracture and mosaicplasty) in 390 patients. The trial has an intended follow-up of 10 years. Although OsCell has shared selected results from this trial in its submissions for this appraisal, no results have been published and the final results are yet to be reported.

### There is some evidence that ACI improves symptoms in the short term

3.6 The committee discussed these 4 trials at its first and second meetings, and noted that the evidence suggested that:

- Over 2 years to 5 years, both MACI and ChondroCelect were more clinically effective than microfracture (improvements in pain and function on the Knee injury and Osteoarthritis Outcome Score [KOOS]).
- At 5 years, the difference in the number of treatment failures and in health-related quality of life between ChondroCelect and microfracture was not statistically significant ( $p \geq 0.05$ ). In contrast, provisional results from the ACTIVE trial suggested that ACI was only clinically beneficial compared with standard treatments (which included microfracture) at 5 years. However, this was based on limited data and, when the committee met for the third time, no data had been published.

In its first 2 meetings, the committee heard conflicting opinions from the clinical experts about the effectiveness of ACI. However, generally the experts considered that there was evidence to show that ACI is clinically effective, although this evidence was not definitive. The committee concluded that, although uncertain, there was some evidence that ACI improves symptoms (based on the KOOS score).

## **It is uncertain how ACI compares with microfracture in the long term**

3.7 The committee noted that the studies originally identified by the assessment group (see [section 3.5](#)) provided limited data on the failure rates of both ACI and microfracture after 5 years. The committee therefore requested that the assessment group review all randomised controlled trials and observational studies that provided outcomes for more than 5 years for ACI and microfracture, including all generations of ACI (that is, ACI available before ChondroCelect, MACI or ACI using cells from OsCell). For the committee's third meeting, the assessment group had broadened its systematic review to include 2 more relevant studies on the failure rates of ACI and microfracture after 5 years in its analyses:

- Nawaz et al. (2014), an observational study of patients' experience with ACI only, at a single English site, over 2 years to 12 years (average follow-up 6.2 years;  $n=827$ ).
- Knutsen et al. (2016), a randomised controlled trial (published since the second committee meeting) comparing ACI with microfracture over 15 years ( $n=80$ ).

## **The assessment group's preferred sources of long-term failure data included Kaplan–Meier data showing time to failure**

3.8 The assessment group's preferred source of data for long-term failure rates of ACI was Nawaz et al. (2014) because the study:

- included more patients than all the other sources of long-term ACI data combined
- reflected UK practice
- provided data on different 'generations' of ACI
- provided data on subgroups.

The committee noted that the available data for long-term failure rates of microfracture were more limited. The assessment group's preferred sources of data were for microfracture were:

- Saris et al. (2009), which reported 3-year Kaplan–Meier data on failure rates in the microfracture arm (n=61) of the TIG/ACT trial (see [section 3.5](#)). The assessment group chose Saris et al. over Vanlauwe et al. (2011), which had 5-year Kaplan–Meier data from the TIG/ACT trial, because the reported data in Vanlauwe et al. did not allow a full analysis of the Kaplan–Meier plot.
- A 15-year follow-up of the microfracture arm (n=40) from Knutsen et al. (2016; see [section 3.7](#)).

All the assessment group's preferred sources of long-term failure data (that is, Nawaz et al. Saris et al. and Knutsen et al.) included Kaplan–Meier data showing time to failure. The committee concluded that these studies were the best available to estimate long-term failure rates of ACI and microfracture.

## **A robust comparison of the long-term effectiveness of ACI and microfracture was not possible with the data available**

3.9 The committee noted that Nawaz et al. (2014), Saris et al. (2009) and Knutsen et al. (2016) used different definitions of ACI failure. Nawaz et al. defined it as a need for reintervention, graft delamination and symptom scores close to or worse than before ACI. Both Saris et al. and Knutsen et

al. defined failure as reintervention only. This meant there were effectively 'more ways to fail' in the Nawaz et al. study than the other 2 studies. As a result, comparing ACI from Nawaz et al. with microfracture from the other 2 studies may have overestimated the failure rate of ACI compared with microfracture. Given this limitation, the committee considered whether it was better to compare the reintervention rates of ACI with microfracture using data from Knutsen et al. However, the committee was concerned that a trial with only 40 people in each arm may have been underpowered to detect a real difference. It also noted that the trial was not done in the UK so may not reflect NHS practice. The assessment group added that the failure rates of microfracture in Knutsen et al. were lower than those in other studies. The committee concluded that a robust comparison of the long-term effectiveness of ACI and microfracture was not possible with the data available.

## **The outcomes may have been confounded by differences in characteristics in patient populations in the trials**

- 3.10 The committee noted that the characteristics of the patient populations in Nawaz et al. (2014), Saris et al. (2009) and Knutsen et al. (2016) may also have differed, which may have confounded the outcomes. In particular, fewer patients in Nawaz et al. had had previous knee surgeries than patients in Saris et al. and Knutsen et al. (34% compared with 77% and 93% respectively). This reinforced the committee's previous conclusion that a robust comparison of the long-term effectiveness of ACI and microfracture was not possible with the data available (see [section 3.9](#)).

## **ACI works better when there has been no previous knee repair and there is no osteoarthritic damage; microfracture is not suitable for defects over 2 cm<sup>2</sup>**

- 3.11 The committee discussed whether there were people for whom ACI or microfracture may work particularly well (or poorly). It noted that, for ACI:

- Stratified data from Nawaz et al. (2014) showed lower failure rates in patients who had no previous knee repair and in people with minimal evidence of osteoarthritis (using Kellgren–Lawrence scores). Larger defect size was not associated with poorer outcomes in these patients.
- A predefined subgroup analysis of the TIG/ACT trial showed lower failure rates in people with symptoms lasting less than 3 years.

For microfracture, it was not possible to determine how previous surgery, the presence or not of osteoarthritis, or duration of symptoms affected the failure rate because of a lack of available stratified data. However, the committee acknowledged the UK clinician consensus that microfracture is less effective in articular cartilage defects over 2 cm<sup>2</sup>, and that ACI should be used in defects of this size (see [section 3.1](#)).

## **Results from the crude (unadjusted) comparison of ACI with microfracture were not robust**

3.12 Given the available evidence and the consensus among UK clinicians, the committee concluded that:

- ACI is likely to be associated with better outcomes if the person has not had previous knee repair or they have minimal osteoarthritic damage associated with the cartilage defect (see [section 3.11](#)).
- ACI is an effective option at this point in the treatment pathway for people with articular cartilage defects over 2 cm<sup>2</sup> (see [section 3.11](#)).
- Limitations in the available subgroup and patient characteristic data meant that an adjustment to account for the differences in the populations between the studies used for estimating the long-term effectiveness of ACI and microfracture was not possible. Because of this, the results from the crude (unadjusted) comparison of ACI with microfracture were not robust.

## **It is unclear whether there are differences in how well different forms of ACI work.**

3.13 The committee considered whether any evidence supported differences in the clinical effectiveness of different ACI interventions (including

different cap or matrix material, or whether or not the chondrocytes were characterised). The committee was aware that the marketing authorisations of ChondroCelect and MACI (before being withdrawn and suspended respectively) differed in the stated defect size. The clinical experts explained that this was because the inclusion criteria for the trials that informed the marketing authorisations differed and that, in clinical practice, the choice of ACI intervention was usually independent of defect size. The committee noted that the indirect comparisons of different forms of ACI did not show differences, but agreed that the included trials may have been too small to detect differences. The clinical experts explained that there was little evidence to suggest that types of ACI differ in their clinical effectiveness. The committee concluded that, although different experts may prefer different forms of ACI, the available evidence did not show a difference in their effectiveness.

## Cost-effectiveness estimates

### The committee used the assessment group's model in its decision-making

- 3.14 In its first 2 meetings, the committee considered the economic models from TiGenix (for ChondroCelect) and the assessment group, noting that their structures were broadly similar. Both used Markov health states that allowed for ACI or microfracture and temporary or permanent success, which predicted the probability of knee replacement. For the committee's third meeting, NICE asked the assessment group to update its model to include data identified from the updated systematic review (see [section 3.7](#)). Because ChondroCelect was no longer being appraised (see [section 3.3](#)) after the first 2 meetings, the committee did not consider the model submitted by TiGenix any further.

### The committee questioned the treatment pathway in the assessment group's model

- 3.15 The committee noted that the updated assessment group's model excluded the possibility of having a second microfracture procedure, such that it now compared ACI followed by ACI or microfracture with



microfracture followed by ACI. However, the committee was concerned that patients in this model could have ACI in each modelled intervention arm (that is, a situation in which ACI was not available was not modelled). The committee noted that only 12% of patients who first had microfracture went on to have ACI. It acknowledged that this lessened the issue, but it would have preferred to have seen a scenario analysis in which patients had either microfracture or ACI, but not both sequentially. The committee heard from the clinical experts that, in clinical practice, clinicians may additionally do an osteotomy, debridement and lavage, before considering a total knee replacement as a final treatment option (see [section 3.1](#)). The committee concluded that the assessment group's model reasonably approximated the treatment pathway in clinical practice, but did not fully reflect it.

## Using longer-term data from separate sources for modelling ACI and microfracture outcomes is still subject to uncertainty

3.16 The assessment group's updated model used new sources of data to model failure rates for ACI and microfracture (see [section 3.8](#)). These sources provided Kaplan–Meier data from which the assessment group reconstructed individual patient-level data using the Guyot method. It tested several parametric curves to extrapolate the data beyond the study follow-up periods, and chose the best fitting based on statistical tests. The assessment group provided results for the cost effectiveness of ACI compared with microfracture for the whole population, for that stratified by previous surgery and osteoarthritic damage (based on Kellgren–Lawrence grade) and for a scenario in which it used extrapolated data from Knutsen et al. (2016) to model both ACI and microfracture. The committee recalled that there were still considerable uncertainties surrounding the effectiveness of both ACI and microfracture because unadjusted data from different sources were used (see [sections 3.8 to 3.12](#)). The committee discussed how these uncertainties may affect the cost-effectiveness estimates:

- The differences in the definition of failure in Nawaz et al. (2014), Knutsen et al. and Saris et al. (2009) (see [section 3.9](#)) may have resulted in an overestimate of the incremental cost-effectiveness ratio (ICER) for ACI compared with microfracture.



- The higher number of patients who had had previous knee surgeries in the studies of microfracture (Saris et al. and Knutsen et al.) than patients in the long-term study of ACI (Nawaz et al.; see section 3.10) may have resulted in an underestimate of the ICER for ACI compared with microfracture.
- It was not possible to determine whether other differences between Nawaz et al. and the microfracture arms of the other trials (see section 3.12) would have resulted in an under- or overestimate of the ICER.
- In the scenario in which Knutsen et al. data were used to model failure rates, the lower failure rates of microfracture in Knutsen et al. than in the other studies (see section 3.9) may have resulted in an overestimate of the ICER.

## **An accurate estimate of the number of people having knee replacements is not possible**

- 3.17 The committee heard from the clinical experts that literature-based estimates of the rates of knee replacement surgery vary widely in people with articular cartilage defects. It noted that there was also uncertainty in how well ACI prevents subsequent total knee replacement compared with microfracture. The committee concluded that the large variance in the probability of knee replacement meant that it was not possible to establish the most plausible estimates to use in the model.

## **Costs in the model**

### **Procedure costs informed by Healthcare Resource Group codes were preferred by the committee**

- 3.18 The committee discussed the costs associated with ACI in the assessment group's model, specifically the cost of cell harvesting and cell implanting. The assessment group had assumed that both the harvesting and implantation procedures would be done as day cases, and the clinical experts agreed with this assumption. In its updated model, the assessment group derived costs from Healthcare Resource Group (HRG) costings: specifically, £870 for cell harvesting (HRG code HB25F) and £2,396 for cell implantation (HRG code HB22C). The

committee concluded that the assessment group's updated model included its preferred procedure costs.

## **The committee heard different estimates of cell costs but used £16,000 as the basis for decision-making**

- 3.19 The committee considered the most appropriate costs of producing and supplying cells. It noted that both the assessment group's model and the ChondroCelect model had assumed a cost of £16,000, which was based on the approximate list prices of ChondroCelect and MACI (when they were available in the UK). However, the committee was aware that companies sometimes provide confidential discounts to the NHS, making the real cost of cells difficult to ascertain. The committee noted that the OsCell submission had estimated a lower cost of £4,125, but this excluded the costs of overheads, and so underestimated the true cost of cells. In response to consultation on the updated assessment report, OsCell had revised the cost of the full procedure including the cells and overheads to £9,266. Although OsCell indicated that start-up costs, including setting up a laboratory for growing cells, were accounted for in its estimate of £9,266, the committee felt that current start-up costs were uncertain and may be higher than what OsCell had estimated. The committee concluded that, although the cost to the NHS of providing the cells for ACI was uncertain, the estimate of £16,000 used by the assessment group and in the ChondroCelect model was reasonable for the purposes of decision-making.

## **Utility values**

### **Utility values in the model for people who had articular cartilage defects appear very low and may not represent the experience of patients in the NHS**

- 3.20 The committee understood that, because of the short trial follow-up, there were limited long-term data on the utility of ACI and microfracture. The assessment group had sourced utility values from a study published by Gerlier et al. (2010), which compared ACI with microfracture using 5-year data from the TIG/ACT trial. The committee noted that Gerlier et

al. lacked information on sample size, missing values and how the authors had mapped the SF-36 data to a health utility index. The committee commented that the utility value before surgery (0.65) seemed low, particularly compared with other similar conditions. The utility values before surgery were even lower in the ACTIVE trial, although the relative changes in utility values were similar to those from TIG/ACT. Over the course of this appraisal, utility data from the SUMMIT trial (measured using the EQ-5D) were published, and reported a utility value before surgery of 0.484. The committee queried why these utilities were so low and heard from a clinical expert that highly active people may perceive cartilage injuries to be particularly disabling. The clinical expert explained that the patients in the trials were young and many were competitive athletes, so would not in general reflect the population considered for ACI in clinical practice. The committee noted that the utility data from SUMMIT showed higher utility values with ACI than with microfracture between week 52 and week 156. Applying these utility values in a scenario analysis rather than the data from Gerlier et al. (which were used in the assessment group's base case) decreased the ICER for ACI compared with microfracture. The committee concluded that there was uncertainty about the modelled utility values and how well they reflected the population considered for ACI in clinical practice. However, it agreed that the most plausible utility values for decision-making were those from Gerlier et al. because these were a less extreme estimate of the impact of cartilage damage on quality of life.

## **Assuming that the utility value of a successful microfracture decreases over time is arbitrary and may favour ACI**

- 3.21 The committee noted that, in its updated model, the assessment group had lowered the utility of microfracture success at year 5 and beyond from 0.82 to 0.65, to reflect evidence that the benefit of microfracture declines after 5 years. The committee noted that this was equivalent to assuming that microfracture had failed in all people at year 5. The committee considered that it would have been preferable to adjust for the reduced efficacy of microfracture more explicitly, by adjusting the transition probabilities instead of the utility of the success health state. The committee agreed that reducing the utility value for microfracture after 5 years was arbitrary and biased the results in favour of ACI. It

noted a sensitivity analysis in which the assessment group set the utility of microfracture success at year 5 and beyond to 0.817 (the same as ACI). This increased the ICER. The committee therefore concluded that removing the assumption that utility decreased over time following a microfracture would likely increase the assessment group's base-case ICER.

## **Utility values for people whose ACI or microfracture is not successful is uncertain, but modelled values are likely to favour ACI**

- 3.22 The committee noted that the assessment group used a utility value for patients who moved to the 'no further repair' health state of 0.69 (that is, patients whose ACI or microfracture had not been successful, but who did not go on to have subsequent surgery). The committee understood that this utility value reflected some benefit from the first procedure, despite it not being successful, and so was not as low as the utility before the procedure (0.65). The committee noted a scenario analysis using utility values, which reflected more benefit after the first procedure than before increased the ICER. The committee concluded that there was uncertainty in estimating utility values for people who did not have subsequent surgery, and that the assessment group's approach favoured ACI.

## **Conclusion**

### **Taking into account the uncertainty surrounding the estimates, the ICER for the whole eligible population may exceed £20,000 per QALY gained**

- 3.23 The assessment group presented the committee with a range of ICERs for ACI compared with microfracture:
- Original and updated base case: £14,000 per quality-adjusted life year (QALY) gained.

- Scenarios in which different data sources were used to model failure rates: £6,000 to £17,000 per QALY gained.
- Only in people who have had previous knee repair surgery: £22,000 per QALY gained.
- Only in people who have not had previous knee repair surgery: £8,000 per QALY gained.
- The ICER was lower than the base case for people who had minimal osteoarthritis in the knee (Kellgren–Lawrence grade 0 or 1) but was higher than the base case for people who had more severe osteoarthritis (Kellgren–Lawrence grade 2 or 3).

The committee noted the numerous uncertainties surrounding the long-term relative effectiveness and utility estimates, and that it was impossible to determine the full effect of all these uncertainties to decide whether any of the ICERs presented by the assessment group were plausible. Additionally, the committee considered that there was a chance that the true ICER may exceed £20,000 per QALY gained for the whole population eligible for ACI in clinical practice. The committee concluded that it was not convinced that the ICER for ACI compared with microfracture was below £20,000 per QALY gained for the whole population eligible for ACI in clinical practice.

## **ACI is recommended for use only in certain subgroups and subject to specific criteria**

3.24 The committee agreed that there was merit in exploring subgroups of patients in whom ACI would be both clinically and cost effective. Based on the evidence presented by the assessment group, and the views of the clinical experts given to the committee, it identified the following subgroups (see section 3.11):

- people who have not had previous knee repair
- people who have minimal osteoarthritic damage to the knee

- people with articular cartilage defects of over 2 cm<sup>2</sup>.

Because the ICER for the subgroup of people who have not had previous knee repair was almost half of that of the entire patient group, the committee agreed that ACI could be cost effective in this subgroup. The committee noted that ACI is generally contraindicated in people with severe osteoarthritis, but the marketing authorisations for traditional ACI and the former marketing authorisations for ChondroCelect and MACI did not define the clinical measure for osteoarthritis (see section 2). The committee noted that Nawaz et al. (2014) had stratified patients in terms of osteoarthritic damage using Kellgren–Lawrence grades. It understood that this grading system was partly subjective, and so decided it was inappropriate to define a cut-off for minimal osteoarthritis using a particular grading system in its final recommendations. Rather, it was appropriate for clinicians experienced in investigating knee cartilage damage to assess suitability for ACI using a validated measure for osteoarthritis of the knee. The committee also noted that its recommendations for use in people with articular cartilage defects of over 2 cm<sup>2</sup> was in line with the published [consensus of 104 UK surgeons](#). It agreed that it is likely that the true ICER for ACI in the population that fulfils all these 3 criteria is likely to be under £20,000 per QALY gained. Finally, the committee noted that, at the time of making these recommendations, the OsCell John Charnley Laboratory was the only provider of ACI in England and that this laboratory is affiliated with a tertiary referral NHS orthopaedic hospital. It considered it appropriate that ACI should only be recommended in the same setting (that is, a tertiary referral centre with specialist expertise) because the evidence for its use in other settings had not been appraised. The committee concluded that it could recommend ACI as a cost-effective use of NHS resources, subject to the criteria in [section 1.1](#).

## Innovation

### Additional consideration of innovation is not warranted

- 3.25 The committee noted that the companies all considered ACI to be innovative, mainly for reasons related to the technical detail of the procedures. The committee agreed that ACI, despite not being new, is technically innovative. However, in the context of a technology appraisal,

innovation needs to be judged in terms of the benefit for patients not captured within the modelling. The committee concluded that it was not possible to surmise that these technologies are innovative in this sense.

## Equality issues

### **The recommendations do not exclude access to ACI for people who are eligible to have it**

3.26 The committee considered its recommendations in the context of the equality legislation. It was aware that one of its criteria for treatment, that is minimal osteoarthritic damage to the knee, excludes people with advanced or severe osteoarthritis, which can be disabling. However, one of the contraindications in the marketing authorisation for the technology is advanced osteoarthritis. In addition, the committee did not stipulate any specific threshold for the level of osteoarthritis, but instead stated in the guidance that it was appropriate for clinicians experienced in investigating knee cartilage damage to assess suitability for ACI using a validated measure for osteoarthritis of the knee. The committee was therefore satisfied that it had mitigated as far as it could any potential unfairness.

## 4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has articular cartilage defects of the knee and the doctor responsible for their care thinks that autologous chondrocyte implantation is the right treatment, it should be available for use, in line with NICE's recommendations.



## 5 Appraisal committee members and NICE project team

### Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

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.

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.

### NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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## Accreditation

