Healthcare Improvement Scotland

NICE Health Technology Appraisal - Assessment Report **Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)**	
TO: NICE **21 January 2015**	**FROM: Healthcare Improvement Scotland**

Comments provided to Healthcare Improvement Scotland, by Mr John Keating, Consultant Orthopaedic Surgeon, Royal Infirmary of Edinburgh

1. I would make some general observations at the outset
2. The natural history of chondral lesions in the knee is not well-established
3. Some of these can be considered as an early stage in the development of generalised osteoarthritis of the knee.
4. However chondral lesions are very common whereas the requirement for total knee joint replacement is not so it is difficult to predict which chondral lesions would progress to the point of symptomatic arthritis requiring knee arthroplasty.
5. The main outcome measures are the Lysholm score, Tegner knee score and Knee Injury and Osteoarthritis Outcome score.
6. The first two are really designed for assessment of knee ligament injury.
7. The Tegner score is a relatively imprecise 10 point score of activity level.

Specific comments

1. The SUMMIT trial compared use of MACI against microfracture. However Genzyme have now been taken over by a North American company and the MACI product has been withdrawn from the European market.
2. The authors review 4 recently published randomised trial comparing microfracture with some form of ACI.
3. Two trials only had a follow-up of 2 years, but showed a modest advantage for ACI.

4. In the TIG/ACT trial of ChondroCelect versus microfracture the differences at 5 years were not significant.

1.3 Interventions

1.3.1 Lavage and debridement.

I would agree that there is currently little evidence to support the use of this intervention for chondral defects in early osteoarthritis of the knee.

1.3.2 ACI

This section is a useful summary of the development of ACI.

1.3.3 Microfracture

This section is rather brief and does not reference much literature on the outcome of microfracture.

1.3.4 Mosaicplasty

I would not necessarily agree that mosaicplasty is little used at the present time. For many institutions it would be the only available alternative to microfracture since there is no general access to ACI.

1.3.5 Conservative management

The studies quoted indicate that the natural history of many chondral defects may well be benign with a low requirement for TKR. The presence of radiographic features of OA at longer term follow-up is perhaps not surprising but the probability of progression to symptoms severe enough to warrant TKR is almost certainly low.

1.4 Decision problem.

As far as I am aware, the Matrix ACI system (MACI® – short for “matrix applied characterised autologous cultured chondrocyte implant”) from Sanofi is no longer on the European market.

2.1 Systematic reviews

The deficiencies of the current literature are well summarised by the various reviews quoted. The findings of these reviews suggest that the evidence to support ACI is either very weak or simply non-existent.

2.1.2 ACI after previous microfracture

The authors review the literature and conclude that prior procedures are associated with a poorer outcome following ACI, particularly microfracture. However this may be because patients who have had prior surgeries are a different group to those presenting early with limited size chondral defects and would do poorly even if ACI was the primary treatment.

2.1.4 Mosaicplasty

The findings in relation to mosaicplasty are somewhat equivocal, with some literature showing superiority of ACI, other publications showing no difference and some showing an advantage for mosaicplasty.

2.2 Trials

2.2.1 Methods

This section discusses trials already previously mentioned in the text.

Chapter 3 - Systematic review of existing economic studies for ACI

The quality of the studies incorporating economic analysis have many compromises in terms of design and the robustness of the data presented and models used are open to question. The authors state in their discussion microfracture requires an inpatient stay, a view with which I would not agree. The Aastrom analysis is very likely to be biased since it is produced by the company marketing one of the products.

Chapter 5 – The cost-effectiveness of autologous chondrocyte implantation

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The authors do not seem to have considered osteotomies around the knee as an option for failed ACI. For localised chondral defects who have failed ACI/microfracture in younger patients an osteotomy would be a preferable option to an arthroplasty. The authors seem to have constructed a very detailed economic model but the problem is that it is based on a lot of assumptions and data from trials with very short follow-up time periods.
In particular I am not convinced that we can assume a high volume of these patients would progress to knee arthroplasty. Some of the analysis assumes that discounted costs for ACI procedures are available. Having negotiated with two of the firms in my roles as clinical director I can confirm the discounts offered were modest, and came with a lot of conditions in relation to numbers of patients we had to treat to qualify for the discounts.

Chapter 6 Discussion

Statement of principal findings

Overall, I would agree with most of the conclusions but I think the authors have taken a fairly optimistic viewpoint of the evidence. There is some more evidence to support the use of ACI based on the most recent trials but in general my interpretation is that because of short term follow-up and methodological flaws in trial design that it is by no means certain that the technique is beneficial in many patients. It remains very expensive and I am unconvinced that even if it is clinically effective in a proportion of

patients that it is a cost effective treatment. I would agree that ACI requires longer term clinical data in particular with more recent innovations to provide better evidence of clinical benefit.

Comments provided to Healthcare Improvement Scotland by: Dr Rajan Madhok, Glasgow Royal Infirmary

Measurements:
Several clinical measures of articular defects are available. Different measurements have been used in each of the four studies. It would be very helpful to know the validity of each and their sensitivity to change. It would also be helpful to know what the minimal meaningful change is with each of the measurements.

Natural History;
Three natural history studies are quoted on page 25. Only one is discussed in detail - in this study after 14 years 21 of 28 had returned to activity and 22 had excellent or good function. No comment is available that any developed radiological or clinical OA .Data from the other two outcome studies would also be helpful to put into context the value of ACI

Outcomes:
One of the outcomes used in the economic model is osteoarthritis requiring a partial or total knee replacement. My understanding is that radiological OA (especially MRI finding) does not correlate with function or symptoms and that the primary indication for a TKR is pain . In the context of the natural history study outlined above it would be helpful to know how an accurate number requiring TKR is determined