Clinical Review Criteria

Autologous Chondrocyte (Carticel®) Implantation for Treatment of Defects in Articular Cartilage of the Knee

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Criteria

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Background

Articular hyaline cartilage is a highly specialized connective tissue that covers the surface of bone in synovial joints. It is a 2-4mm thick hyaline cartilage that provides smooth low friction movement and shock absorption. Unlike most tissues, articular cartilage does not have blood vessels, nerves, or lymphatics. It is composed of a dense extracellular matrix (ECM) with a sparse distribution of highly specialized cells called chondrocytes. The ECM is principally composed of water, collagen, and proteoglycans, with other non-collagenous proteins and glycoproteins present in lesser amounts. These components help to retain water within the ECM, which is critical to maintain the unique mechanical properties of the cartilage (Fox 2009, Negrin 2013, Oussedik 2015).

The articular cartilage is prone to damage from acute high energy trauma and from repetitive shear and torsional forces applied to the surface. Lesions to the articular cartilage are often associated with pain and compromised joint function, and may lead to the development and progression of osteoarthritis. The damaged cartilage has very limited capacity for self-repair due to its avascular and hypocellular nature. Surgery has thus been the standard approach for repairing articular cartilage damage. Surgical techniques intended for restoring the articular surface are classified into 3 categories: 1. Marrow stimulation procedures such as microfracture, 2. Cell-based implantation, and 3. Osteochondral grafting. Surgical interventions have also been categorized as 1. Reparative, which includes marrow stimulation such as microfracture; drilling; and abrasion arthroplasty, and 2. Reconstructive that includes allograft transplantation; osteochondral autograft transplantation (OAT); and autologous chondrocyte implantation (ACI). Investigators suggest that microfracture surgeries is more effective than reconstructive
surgical procedures for the repair of smaller cartilage defects (<100mm2) while reconstructive surgeries are more effective for larger defects (>100mm2) (Crawford 2012, Perera 2012, Negrin 2013, Mundi 2015, Li 2015).

Currently, marrow stimulation through microfracture is the standard first-line surgical treatment for articular cartilage lesions of the knee. The microfracture technique was developed by Steadman in the early 1980s. It is a single-stage arthroscopic procedure that involves penetrating the subchondral bone plate after removing the damaged hyaline cartilage. Bleeding from the subchondral bone forms a clot that attracts bone marrow cells to migrate into the cartilage defect and create a ‘super clot’ that eventually matures into a firm repair tissue consisting of a combination of fibrous and hyaline-like cartilage. The technique is minimally invasive, technically simple, and is associated with low morbidity. However, the repair is composed of fibrocartilaginous tissue, which is mechanically inferior to the native hyaline cartilage; it has less ability to withstand shock and shearing forces leading to deterioration in function over time. In addition, the bone marrow stem cells and growth factors are released into the joint rather than being contained in the site of the defect. Some researchers suggest that microfracture is more effective in reducing pain and improving joint function when performed for new injuries, small focal injuries, and in younger individuals with lower body mass index (Crawford 2012, Negrin 2013, Lee 2014, Mundi 2015).

Osteochondral autograft transfer (OAT), also known as osteochondral cylinder transplantation or mosaicplasty, is a whole tissue transplantation procedure that was developed in the 1990s for hyaline cartilage repair. It is a surgical technique that uses osteochondral grafts taken from the lighter-load bearing areas of the patient’s own joint to fill the focal defects. There is a concern however, with the donor site morbidity, and thus the technique may not be recommended for lesions larger than 400mm2 (Li 2015, Mundi 2015).

Autologous chondrocyte implantation (ACI), also known as autologous chondrocyte transplantation, is a cell-based method that was introduced in the late 1980s for the treatment of symptomatic full thickness cartilage defects of the knee. The first generation of ACI (ACI-P) is a two-stage procedure. First, a cartilage biopsy is harvested from healthy cartilage of the affected knee during an arthroscopic biopsy procedure. The specimen of live articular cartilage is sent to a cell expansion laboratory for chondrocyte culture. The cells are separated from the cartilage under a strictly controlled environment, and then multiplied using a cell-culture technique for 3-6 weeks. The cultured chondrocytes are then implanted into the cartilage defect in an open arthrotomy procedure. This procedure involves removing a periosteal flap from the proximal medial tibia, suturing it to the surrounding rim of normal tissue, and implanting the expanded chondrocytes beneath the flap to start filling the defect by producing a matrix. Unlike the MS techniques, it is reported that ACI has the ability of repairing the defect by a hyaline-like cartilage with a hybrid of fibrocartilage and hyaline like tissue, or with fibrocartilaginous material containing type-1 and type II collagen. ACI-P is an invasive, technically complicated procedure that involves two operations, has a long recovery time, and requires extensive post-surgical rehabilitation. The technique has variable success rate and may be associated with periosteal hypertrophy and overgrowth that would require additional surgeries (Crawford 2012, Niemeyer 2014, Mundi 2015).

Several modifications to the first generation ACI-P have been made to reduce the procedural technical demands associated with the tissue harvest and the use of periosteal flap in order to decrease the surgical morbidity and prevent periosteal hypertrophy and overgrowth. These modifications were described as second and third generations. The second generation ACI (ACI-C) uses bioengineered bilayer collagen covers to substitute for the periosteal flap and avoid the spill over and asymmetric distribution of chondrocytes following implantation. The third generation ACI explores the use of biomaterials to construct a 3-dimensional scaffold for chondrocyte implantation; the all-in-one grafts do not need a periosteal cover or fixing stitches and can be trimmed to fit the cartilage defect with fibrin glue. It has been reported that implantation of third generation ACI can be performed arthroscopically or with a small incision (Vasiliadis 2010, Kuroda 2011, Crawford 2012, Negrin 2013, Mundi 2015, Samsudin 2015).

Medical Technology Assessment Committee (MTAC)

Autologous Chondrocyte Implantation

02/14/2001: MTAC REVIEW

Evidence Conclusion: The existing evidence is not sufficient to determine the effect of ACI on health outcomes. The only data available are from case series report that have compromised validity and are not considered to provide high quality data. Each of the two case series articles evaluated had additional limitations beyond study type including providing little information about possible adverse effects. Peterson and colleagues are involved with a prospective randomized trial of autologous chondrocyte transplantation compared to periosteum alone or subchondral drilling for the treatment of primary chondral lesions of the femoral condyle. Results of this study will provide higher-quality data.
The use of Autologous Chondrocyte (Carticel®) Implantation for Treatment of Defects in Articular Cartilage of the Knee does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

04/17/2003: MTAC REVIEW

**Autologous Chondrocyte Implantation**

**Evidence Conclusion:** There were two small randomized controlled trials (Bentley et al, n=100.; Horas et al., n=40). Neither provided strong evidence that autologous chondrocyte implantation is superior to an alternate procedure for repairing osteochondral defects in the knee. The Bentley study was larger and had stronger methodology. The authors found that the overall clinical results did not differ significantly between groups (autologous chondrocyte implantation compared to mosaicplasty), but that, among the 51 patients with medial femoral defects, the autologous chondrocyte group had better post-operative knee function. The one-year arthroscopic data in the Bentley study was compromised because 40% of patients were missing from the analysis. The Horas study had inadequate randomization and several additional threats to validity. They found worse post-operative knee instability in the autologous chondrocyte transplantation group compared to a group receiving autologous osteochondral cylinder transplantation and no significant differences between groups on the two other primary measures.


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07/14/2004: MTAC REVIEW

**Autologous Chondrocyte Implantation**

**Evidence Conclusion:** The evidence consists of three controlled trials (2 randomized, 1 pseudo-randomized), all comparing autologous chondrocyte implantation to other surgical procedures to restore articular cartilage. There are no sham controlled studies. None of the studies found significantly better clinical outcomes with ACI compared to the alternative intervention 1-2 years post-surgery; some may have been underpowered. Knutsen et al, the strongest study methodologically, found better results for the group receiving microfracture on one key outcome, the physical component score of the SF-36. The Bentley study found better histological results in the ACI group, but this analysis included only 60% of the randomized patients. In summary, ACI does not provide a clear clinical advantage over other surgical procedures to heal cartilage injuries and may be inferior to microfracture.

**Articles:** The Medline search yielded 42 articles, many of which were on technical aspects of the procedure or on related technologies. There were three randomized controlled trials and all three were critically appraised. References are as follows: Knutsen G, Engbretsen L, Ludvigsen TC. Autologous chondrocyte implantation compared with microfracture in the knee. *J Bone Joint Surg* 2004; 86-A: 455-464. See Evidence Table.

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06/05/2006: MTAC REVIEW

**Autologous Chondrocyte Implantation**

**Evidence Conclusion:** One new RCT compared autologous chondrocyte implantation to an alternative procedure. The study (Dozin et al., 2005) did not find a significant difference in the clinical success rate of patients who received ACI or mosaicplasty. The study was underpowered to detect a clinically meaningful difference between groups due to low compliance rate. Only 12/22 (54%) in the ACI group and 11/22 (50%) in the mosaicplasty group actually received the surgery, which occurred 6 months after an initial debridement. The best evidence on ACI for treatment of defects in articular cartilage of the knee remains the randomized controlled trials.
reviewed in 2004. The conclusion from the previous MTAC report was: The evidence consists of three controlled trials (2 randomized, 1 pseudo-randomized), all comparing autologous chondrocyte implantation to other surgical procedures to restore articular cartilage. There are no sham controlled studies. None of the studies found significantly better clinical outcomes with ACI compared to the alternative intervention 1-2 years post-surgery; some may have been underpowered. Knutsen et al, the strongest study methodologically, found better results for the group receiving microfracture on one key outcome, the physical component score of the SF-36. The Bentley study found better histological results in the ACI group, but this analysis included only 60% of the randomized patients. In summary, ACI does not provide a clear clinical advantage over other surgical procedures to heal cartilage injuries and may be inferior to microfracture. A 2005 technology assessment conducted by the National Institute for Health and Clinical Effectiveness (NICE) in England concluded that there is inconsistent evidence on the clinical effectiveness of ACI and did not recommend ACI except in the context of ongoing clinical trials.

**Articles:** Three new randomized controlled trials were identified. Two trials, one by Bartlett and colleagues and the other by Gooding and colleagues, were not evaluated further because they compared two types of autologous chondrocyte replacement and did not include a control group that received an intervention other than ACI. (In addition, the Gooding study was only available as an abstract). The other trial compared ACI and mosaicplasty and was critically appraised: Dozin B, Malpeli M, Canceldo R et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty. Clin J Sport Med 2005; 15: 220-226. See Evidence Table.

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**03/21/2016: MTAC REVIEW**

**Autologous Chondrocyte Implantation (Autologous Chondrocyte Transplantation) For the Treatment of Chondral Defects in the Knee**

**Evidence Conclusion:** Autologous chondrocyte Implantation (Carticel, the first generation) was previously reviewed by MTAC, four times between 1998 and 2006. At the time the best published evidence consisted of four controlled trials (three randomized and one pseudo-randomized), none of which found significantly better clinical outcomes with ACI compared to the alternative interventions at 1-2 years post-surgery. Knutsen et al (2004), the strongest study methodologically, at the time, found better results for the group receiving microfracture on one key outcome (the physical component score of the SF-36). The Bentley et al's study (2003) found better histological results in the ACI group, but the analysis included only 60% of the randomized patients. In summary the 2006 report concluded that ACI does not provide a clear clinical advantage over other surgical procedures to heal cartilage injuries and may be inferior to microfracture. The updated literature search for the current re-review of ACI, identified a number of published comparative and non-comparative studies evaluating the effectiveness of ACI, marrow stimulation (MS, mainly with MF techniques), and OAT, in improving the clinical outcomes of patients with cartilage lesions in the knee. Different ACI generations and techniques were evaluated and/or compared to other interventions used for restoring knee function. The published studies were relatively small, and in addition to the variations in the surgical techniques and approaches used for ACI and other procedures, there were differences between the studies in the criteria for patient selection, lesion sizes, outcomes, duration of follow-up, and measures used to evaluate histological and/or functional outcomes. In addition none of the trials was blinded and pain and function measures mainly relied on subjective evaluation, which may bias the results. Few studies showed minimal differences between ACI compared to MF, or OAT, and many others found no significant differences in outcomes with the different surgical techniques. The majority of the studies were underpowered to detect statistical differences, and a lack of significant differences between procedures does not necessarily indicate that they are equivalent or have similar effects. Combining the studies into meta-analyses increases the power, but the significant heterogeneity between the published studies on the treatment of chondral lesions in the knee precluded pooling the results of the individual studies in many cases, and/or performing subgroup analyses to determine the optimal procedure to the patient according to the lesion size, type of activity, comorbidity, and other characteristics. Few authors cautiously pooled the results of studies into meta-analyses, but these have to be interpreted with caution as the results of a meta-analysis are as good as the quality of the studies it includes.

**ACI versus microfracture (MF):** Mundi and colleagues (2015) (Evidence Table 1), performed a systematic review and meta-analysis of RCTs to compared ACI, MF, and OAT. The authors could only pool the results of the studies comparing ACI versus marrow stimulation (MS), mainly using the microfracture (MF) technique. The meta-analysis had valid methodology and analysis, but the included studies had their limitations, and were significantly heterogeneous. The overall pooled results showed no significant difference between ACI and MF in improving knee function and pain at intermediate-term follow-up. Oussedik and colleagues (2015) performed a systematic review to compare the outcomes of MF and ACI in patients with articular cartilage lesions of the knee. The review included 34 articles only 9 of which were comparative studies, the rest were observational with no control groups, and 2 were animal model studies. The authors could not pool the results of the comparative studies into a meta-analysis due to the significant heterogeneity between the studies. They concluded that low quality (grade IV) evidence suggests that MF may be effective in smaller lesions and is usually associated with a greater proportion...
of fibrocartilage production which may affect its durability. They also suggested that the multiple lesions treated with MF have poorer outcomes compared with single lesions. ACI was an effective treatment that may result in a greater proportion of hyaline-like tissue at the repair site, appears to be effective for larger lesions. The authors noted however, that the variation in techniques and modifications used for repairing chondral lesions of the knee, together with the different outcomes and measures used, and lack of long-term follow up make it hard to compare techniques and/or determine the optimal procedure for the different patient groups. Negrin and colleagues (2013) (Evidence Table 2), conducted a systematic review and meta-analysis to compare the clinical outcomes of MF and ACI after equal follow-up periods. The review included 7 RCTs and 2 observational studies with at least one year follow-up. The meta-analysis had some disadvantages which may limit generalization of its results. It included a small number of studies with relatively small population sizes, and the authors pooled the results of the RCTs together with the observational studies that used different scores and values for assessing the outcomes. They performed two meta-analyses: the first included all three ACI generations, and the second only included the second and third generations. The first analysis showed a small statistically insignificant difference between MF and all three ACI generations combined after 1 year, and the second meta-analysis showed a significant improvement with ACI after the first generation study (Knutsen et al, 2007) was excluded. The authors noted however, that the observed statistically significant difference was clinically irrelevant. They indicated that the two procedures are complementary, and that large RCTs with long-term follow-up are needed to determine which groups of patients would benefit more from each procedure. Vanlaauwe J, and colleagues (2011) published 5-year follow up results of an earlier study (Saris et al, 2008) that compared ACI using characterized chondrocyte implantation (CCI) (ChondroCelect, Belgium) vs. MF in 118 patients with a single symptomatic cartilage defect in the knee. The study had 90% power to detect a significant difference in the success rate between the two techniques. The first article reporting the results of one-year follow up showed significant clinical improvement with the two techniques when compared to baseline. There were no significant differences between the two procedures in the short-term clinical outcomes or complication rates, but the tissue regenerate was superior with ACI. The published 5-year results showed that the clinical improvements reported at 12 months and 24 months were maintained for the duration of follow-up. There were no significant differences between the two groups in clinical outcomes, radiological outcomes, or treatment failures. However, the latter tended to occur earlier with MF (in those treated in less than 3 years from onset of symptoms). Subgroup analyses showed no significant differences by age (at 35 years cutoff), and that females had more treatment failures irrespective of the procedure they underwent. Knutsen and colleagues’ (2007) long-term follow-up results of the RCT that compared first generation of ACI vs. MF (published in 2004 and reviewed earlier by MTAC) showed no significant difference between the two techniques in the clinical or radiological outcomes at 5 years posttreatment. There was a 23% failure rate (need for a reoperation due to lack of healing) in each of the treatment groups at 5 years compared to only 2.5% failures in the MF and 5% with ACI at 2 years. Younger patients (<30 years of age) had better outcomes than older patients irrespective of the treatment group. One third of the patients had radiographic evidence of early osteoarthritis at 5 years. The authors noted that the study was limited by only including patients with chronic symptomatic cartilage defect of the knee, and by the lack of a control group that did not undergo surgical treatment or who were simply treated with arthroscopic lavage. The authors concluded that further long-term follow-up is needed to determine if one method is superior to the other, and to study the progression of osteoarthritis. ACI versus Osteochondral autograft transplantation (OAT) Li et al, 2015 (Evidence Table 3) performed a systematic review and meta-analysis of RCTs to compare the efficacy of OAT versus ACI in the treatment of large cartilage defects of the knee. The analysis included 5 relatively small trials two of which evaluated the same cohort at different time periods. There were differences between the studies in the surgical techniques and scoring of outcomes. The authors quantified the results into crude grades for comparisons. The overall pooled results of the trials, after performing a sensitivity analysis suggest that there were no significant differences between OAT and ACI results in the short-term, but ACI has superior outcomes on the long-term. Patients undergoing OAT were more likely to have worse conditions on the long-term when compared to those receiving ACI. The authors explained that the injuries for autografts in OAT, the absence of fill and difference in orientation may influence the patient outcomes and limit further OAT procedures. On the other hand ACI can be performed repeatedly in the same patient using tissue engineered material. Clave, et al (2016), randomized 55 patients with isolated symptomatic femoral osteochondral defects 2.5-7.5 cm² to receive Cartipatch (third generation ACI) or mosaicplasty (OAT). Patients were followed-up or 2 years, and the primary outcome measure was the change in the functional outcome from baseline to month 24 postoperatively. This was subjectively measured by International Knee Documentation Committee (IKDC) score. The investigators could only recruit 55 of the 76 (72%) patients needed to provide sufficient power, 15% of those randomized were lost to follow-up, and only 54% were included in the analysis. The authors indicated that contrary to the hypothesis of the study, the results showed that mosaicplasty was superior to Cartipatch in improving IKDC score 2 years after surgery. The significant difference between the two procedures was observed for defects measuring ≥ 3.5 cm². No significant difference was observed for smaller lesions. The trial was randomized and controlled, but had several disadvantages that would limit generalization of its results. It was small in size, the patients were not blinded to the procedure they underwent, only 55% of those randomized were included in the analysis, the outcome was subjective, and the follow-up duration was insufficient to determine
the long-term outcomes of the interventions. Bentley and colleagues, 2012 (included in Li et al's 2015 meta-
analysis discussed earlier) published 10-year results of an earlier RCT that compared ACI to mosaicplasty among
100 patients with chronic lesions. The mean articular cartilage lesion size was 440.9 mm² (range 100-1050 mm²)
in the ACI group, and 399.6 mm² (100-2000 mm²) in the mosaicplasty group. The early results of the trial showed
significantly better outcome with ACI at 18 months post-surgery. This has been sustained over the years. At ten
years, the functional outcome was significantly better with ACI vs. mosaicplasty when measured by the Cincinnati
score, but insignificant with Stanmore-Bentley score. It is to be noted however, that only 15 of 48 patients
randomized to OAT were included in the 10-year assessment of function. The failure rate (needed revision
operations) was significantly higher in the mosaicplasty group vs. the ACI group (55% and 17% respectively). The
pattern of failure was different; the ACI showed a low steady failure rate across 10 years, while the mosaicplasty
group remained relatively satisfactory for the first 2 years then experienced a steep failure rate over the next 2
years. **ACI versus any other treatment for articular cartilage lesions** Vasiliadis and colleagues, 2010
conducted a systematic review of RCTs and quasi-randomized trials to compare ACI with any other type of
treatment (including no treatment or placebo). The authors could not pool the results into a meta-analysis due to
the clinical and methodological heterogeneity between the studies. They concluded that the studies show that ACI
is an effective treatment for full thickness chondral defects and associated with improvement in clinical outcomes
compared to baseline. The published evidence however, does not suggest any superiority of ACI over other
treatments; complications rates were comparable between the different interventions except with an increased
graft hypertrophy with ACI-P (the first generation ACI). Mundi and colleagues (2015) (Evidence Table 1),
 systematic review and meta-analysis of RCTs (discussed earlier) compared ACI; marrow stimulation (MS mainly
using MF), and OAT to determine whether a single technique has superior outcomes at an intermediate follow-up
period. The review included 11 RCTs (published through April 2014) with a total of 765 patients. 5 trials compared
ACI vs MS, 3 compared ACI vs. OAT, and 3 evaluated different generations of ACI. The authors could only pool
the results of the RCTs comparing ACI versus MS and found no significant difference between the two procedures
in improving function or reducing pain at intermediate term follow-up. They indicated that ACI, MS, and OAT are all
generally efficacious in improving symptoms in patients with focal knee cartilage defects, The authors pointed to
the limitations and heterogeneity of the published studies and noted that the current best evidence does not show
that any of the three techniques is superior to the others in improving the intermediate-term pain and function.
They concluded that high quality studies with sufficient power and long-term outcomes are needed before any
specific intervention is recommended over others. Samsudin and Kamural (2015) conducted a systematic review
to compare different generations of ACI to other treatment modalities. Like many other researchers, they could not
pool the results of the trials into a meta-analysis due to the heterogeneity between the studies. They concluded
that the literature shows a trend towards similar outcomes when comparing ACI generations with other repair
techniques, and that there is insufficient evidence to conclude that that ACI and it newer generations are more
effective than other techniques in in repairing articular cartilage defects of the knee. Conclusion: There is
insufficient published evidence from adequately powered large RCTs with valid methodology and long-term follow-
up duration to determine that ACI and its newer generations are superior to other surgical techniques in repairing
articular defects of the knee. The variations between the published studies make it difficult to accurately compare
one intervention versus another or to determine the optimal procedure and technique for the individual patient. The
literature suggests, but does not provide sufficient evidence that the newer generations of ACI may be associated
with better long-term outcomes compared to microfracture in patients with larger full thickness, focal chondral
defects in the knee.

**Articles:** The literature search revealed a large number of experimental and observational studies on autologous
chondrocyte implantation. Several small randomized controlled studies compared one or more generation ACI with
MF, with OAT, or versus another ACI generation. The search also identified a number of systematic reviews with
or without meta-analyses on ACI compared to one or more of the other treatment modalities. The more recent
meta-analysis comparing ACI with microfracture (Negrin, 2013), a meta-analysis comparing ACI to OAT (Li, 2015),
an analysis comparing all three procedures (Mundi, 2015) were selected for critical appraisal. Studies comparing
one generation ACI to another generation were excluded from the review. Mundi R, Bedi A, Chow L, Crouch S3
2015 Jul 2. pii: 0363546515589167. **See Evidence Table.** Negrin LL, Vécsei V. Do meta-analyses reveal time-
dependent differences between the clinical outcomes achieved by microfracture and autologous chondrocyte
Table.** Li Z, Zhu T, Fan W. Osteochondral autograft transplantation or autologous chondrocyte implantation for
large cartilage defects of the knee: a meta-analysis. Cell Tissue Bank. 2015 Jun 12. **See Evidence Table.**

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### Revision History

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<th>Date</th>
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<td>04/05/2016</td>
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### Codes

- **CPT**: 27412
- **HCPCS**: J7330, S2112