

# Advances in the Surgical Management of Articular Cartilage Defects: Autologous Chondrocyte Implantation Techniques in the Pipeline

Spencer Stein<sup>1</sup>, Eric Strauss<sup>1</sup>, and Joseph Bosco III<sup>1</sup>

## Abstract

**Objective:** The purpose of this review is to gain insight into the latest methods of articular cartilage implantation (ACI) and to detail where they are in the Food and Drug Administration approval and regulatory process. **Design:** A PubMed search was performed using the phrase “Autologous Chondrocyte Implantation” alone and with the words second generation and third generation. Additionally, clinicaltrials.gov was searched for the names of the seven specific procedures and the parent company websites were referenced. **Results:** Two-Stage Techniques: BioCart II uses a FGF2v1 culture and a fibrinogen, thrombin matrix, whereas Hyalograft-C uses a Hyaff II matrix. MACI uses a collagen I/III matrix. Cartipatch consists of an agarose-alginate hydrogel. Neocart uses a high-pressure bioreactor for culturing with a type I collagen matrix. ChondroCelect makes use of a gene expression analysis to predict chondrocyte proliferation and has demonstrated significant clinical improvement, but failed to show superiority to microfracture in a phase III trial. One Step Technique: CAIS is an ACI procedure where harvested cartilage is minced and implanted into a matrix for defect filling. **Conclusion:** As full thickness defects in articular cartilage continue to pose a challenge to treat, new methods of repair are being researched. Later generation ACI has been developed to address the prevalence of fibrocartilage with microfracture and the complications associated with the periosteal flap of first generation ACI such as periosteal hypertrophy. The procedures and products reviewed here represent advances in tissue engineering, scaffolds and autologous chondrocyte culturing that may hold promise in our quest to alter the natural history of symptomatic chondral disease.

## Keywords

chondrocytes, cells, articular cartilage, tissue, cartilage repair, repair, autologous chondrocyte, grafts

## Introduction

Our aging, physically active population has resulted in a high prevalence of articular cartilage defects.<sup>1,2</sup> These defects, if left untreated, can result in premature degenerative arthritis. The appropriate management of articular cartilage defects remains an unsolved problem. The biology of human articular cartilage precludes repair as chondrocytes, although metabolically active, do not have the ability to respond to or repair local injuries. The inability of articular cartilage to heal was first described by Scottish physician William Hunter who, in a paper presented to the Royal Medical Society stated, “an ulcerated cartilage is a troublesome problem and once destroyed, it never repairs.” Today, although many treatment options are available, none have resulted in the complete regeneration of 3-dimensional articular cartilage.

To address the limitations of current chondrocyte-based cartilage repair techniques, recent advances have been made

leading to the development of second- and third-generation autologous chondrocyte implantation (ACI) techniques for the management of symptomatic chondral lesions. These newer generation ACI methods make use of 3-dimensional matrices that eliminate the need for periosteal flaps. Other innovative technologies that allow for the immediate implantation of harvested chondrocytes, thus eliminating the need for a second procedure, have also been devised. In this review, we describe 7 new techniques for articular cartilage defect repair. These methods are not currently approved by the Food and Drug Administration for use in the United States but have shown promising results in clinical trials in and outside the United States.

---

<sup>1</sup>NYU Hospital for Joint Diseases, New York, NY, USA

### Corresponding Author:

Joseph Bosco III, NYU Hospital for Joint Diseases, C/O Lorraine H. Hutzler, 301 East 17th Street, New York, NY 10003, USA  
Email: lorraine.hutzler@nyumc.org

## Methods

A PubMed search was performed using the phrase “Autologous Chondrocyte Implantation” alone and with the words second generation and third generation. PubMed and clinicaltrials.gov were searched for the names of the 7 specific procedures (BioCart II, MACI, Cartipatch, NeoCart, Hyalograft-C, ChondroCelect, CAIS.). Additionally, the 7 individual company websites were examined for information pertaining to Food and Drug Administration status. For the purpose of this review, we divided the 7 methods into procedures requiring 2 separate operative procedures (2-step) and 1 operative procedure (1 step).

## Two-Step Procedures

### *BioCart II (Histogenics Corporation, Waltham, MA)*

The BioCart system uses a laboratory protocol where autologous chondrocytes harvested arthroscopically are cultured with autologous human serum and a cell growth factor, FGF2v1. The cells are then isolated and seeded into a fibrin-hyaluronan matrix (plasminogen-free fibrinogen and thrombin with hyaluronic acid), which is implanted into the cartilage defect in a second surgical procedure using a mini-arthrotomy.<sup>3,4</sup>

Preliminary studies have demonstrated the feasibility of the implantation procedure and the lack of adverse events at 1-year follow up. Clinical improvement based on Lysholm and International Knee Documentation Committee (IKDC) scores<sup>5</sup> have also been documented.<sup>4</sup> Additionally, evidence based on T2-mapping and dGEMRIC analysis demonstrated repair tissue similar to hyaline cartilage.<sup>6</sup> More recently, Eshed *et al.*,<sup>8</sup> reported on 31 patients (24 female and 7 male), with a mean age of 33.6 years who were evaluated at a mean time of 17.3 months postoperatively. All the patients received BioCart II for a single full thickness cartilage defect of the femoral condyle secondary to trauma or osteochondral defect. The results showed clinical improvement using IKDC score, morphological improvement using MRI and MOCART<sup>7</sup> scoring for patients with a smaller implant size (<3 cm<sup>2</sup>) and biochemical evidence using T2-mapping that showed distinct organizational layering typical of hyaline cartilage.<sup>8</sup> The limitation to the 2011 article by Eshed *et al.* is that as a cross-sectional retrospective analysis, it lacks preoperative/baseline MRI and does not compare the results following BioCart II to a control group.

Currently, BioCart II is available in Israel. A multicenter phase II clinical trial in the United States comparing BioCart II with microfracture is underway, with an estimated study completion date of May 2015.<sup>9</sup>

### *Matrix-Induced ACI (Sanofi US, Bridgewater, NJ)*

Matrix-induced ACI (MACI) is a 2-stage procedure where cartilage is harvested from a non-weight-bearing region and sent for chondrocyte isolation, proliferation, and seeding into a biodegradable scaffold over a 4-week period. MACI's implant consists of a purified and cell-free porcine collagen I/III membrane. One side of the membrane is compact and is implanted facing into the joint, whereas the other side is porous (to offer an environment for cell seeding) and is implanted facing the bottom of the lesion.<sup>10</sup> Once the implant has been prepared, it can be glued into the chondral defect through a mini-arthrotomy. Commonly, a fibrin glue is used to seal the implantation site.<sup>11-13</sup>

The composition and design of the MACI implant was postulated to improve tissue quality and outcomes as compared with first-generation ACI. Complications due to the periosteal flap used in the original ACI technique include the need to harvest periosteum from the tibia and suture the flap into healthy articular cartilage, the uneven distribution of chondrocytes under the flap, graft failure, delamination, and periosteal hypertrophy.<sup>14-16</sup> A small randomized control trial compared the original ACI with MACI and reported that although MACI was not superior to the original ACI in clinical scores, MACI repaired lesions had more homogeneous repair tissue than did first generation ACI repaired defects on MRI imaging.<sup>14</sup>

A prospective randomized study compared MACI with ACI with a collagen cover (ACI-C). ACI-C was thought to be an improvement on the first generation ACI. This study showed significant improvement in reported scores with both MACI and ACI-C but no significant difference between the 2 methods.<sup>17</sup> In the most recent prospective clinical study, Basad *et al.*,<sup>18</sup> randomized 60 patients, aged 18 to 50 years, to MACI versus microfracture, and followed them over a 2-year period. They reported that MACI was significantly more effective than microfracture after 24 months, although both groups had significant improvement from baseline.<sup>18</sup> This study used Tegner,<sup>19</sup> Lysholm,<sup>20</sup> and ICRS (International Cartilage Repair Society)<sup>21</sup> scores in their outcome assessment. The major limitation to the study is the subjective nature of the self-reported surveys used to evaluate improvement of the knee joint. MRI was not used as part of the protocol to evaluate the grafted area.

Currently, MACI is available in Europe, Asia, and Australia.<sup>22</sup> Recently, Sanofi announced that MACI showed significant improvement versus microfracture in a primary endpoint, with preliminary results to follow in early 2013.<sup>23</sup> This is a randomized, open-label, parallel-group, multicenter study in 144 patients aged 18 to 55 years. The aim of the study is to follow patients up to 5 years and to document adverse events, functional and pain outcomes, arthroscopic

and histologic evaluation, and MRI. Patients will continue to be followed by an extension trial that has an estimated completion of May 2015.<sup>24</sup>

### **Cartipatch (Tissue Bank of France, Lyon, France)**

Cartipatch is another 3-dimensional scaffold that requires arthroscopic cartilage harvest, laboratory isolation and culture, and follow-up mini-arthrotomy.<sup>25</sup> Cartipatch's chondrocyte suspension scaffold consists of an agarose-alginate hydrogel.<sup>25,26</sup> Advantages of this approach include the ability of the hydrogel to mold to the shape of the defect and the even distribution of chondrocytes within the implant.<sup>10</sup> A phase II prospective multicenter clinical trial reported on 17 patients, ages 17 to 42 years, who underwent the Cartipatch procedure and were followed for 2 years. The outcomes were measured with IKDC score,<sup>5</sup> postoperative MRI, ICRS arthroscopic score,<sup>27</sup> histologic O'Driscoll,<sup>28</sup> and ICRS<sup>27</sup> score at final follow-up. The study reported significant improvement in subjective score and a significant decrease of the defect size on MRI. Arthroscopic evaluation showed 11 out of 13 patients with normal to nearly normal findings and histological assessment showed predominantly hyaline-like cartilage in 8 out of 13 patients. There was a strong correlation between subjective IKDC clinical score and ICRS arthroscopic score, but no correlation could be established between IKDC clinical score and histologic score.<sup>25</sup> The limitations to the study are the lack of comparison with a standard control technique and the small sample size. In addition, the MRI evaluation was not scored using an established scoring system such as MOCART.<sup>7,29</sup>

Currently, Cartipatch is in a phase III trial being conducted in France, where it is being compared to Mosaicplasty, which had an estimated completion date of December 2012.<sup>30</sup> Another phase III trial in Europe comparing Cartipatch to microfracture has not yet completed patient recruitment.<sup>31</sup>

### **NeoCart (Histogenics Corporation, Waltham, MA)**

The NeoCart implant is a bovine type I collagen 3-dimensional honeycomb matrix. The chondrocyte culturing procedure is unique in that the seeded implant is further processed in a bioreactor in "exacting conditions of high pressure, oxygen concentration and perfusion."<sup>32</sup> The culture conditions aim to mimic the environment of the knee in order to encourage chondrocytes to synthesize glycoproteins. The laboratory procedure, as described, required 6 to 9 weeks.<sup>33,34</sup>

A phase I trial reported no major adverse events, a significant decrease in the visual analogue score, improvement in IKDC score in 7 of 8 patients, an increase in knee range

of motion in 7 of 8 patients, and good to complete defect fill in 6 of 8 patients on MRI performed at 2-year follow-up.<sup>33</sup> Recently, Crawford *et al.*,<sup>34</sup> published the results of a phase II randomized control trial comparing 21 patients treated with NeoCart with 9 patients treated with microfracture. After 24 months, patients who received NeoCart had significantly greater improvement than those who were treated with microfracture based on IKDC, visual analogue score, Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and sports scores. The study did not, however, look at histological or image based outcomes.

Currently, a phase III trial is underway in the United States. It aims to randomize 245 patients to NeoCart or microfracture and has an estimated completion date of March 2015.<sup>35</sup>

### **Hyalograft C Autograft (Anika Therapeutics, Bedford, MA)**

Hyalograft C is a 3D nonwoven graft consisting of an esterified derivative of hyaluronic acid, known as Hyaff 11 (Anika Therapeutics, Bedford, MA).<sup>36</sup> The proponents of Hyalograft C point to data demonstrating that chondrocytes seeded on Hyaff 11 produce collagen type II and aggrecan, which are components of articular cartilage.<sup>37</sup> According to Anika Therapeutics, the Hyaff-based scaffold spontaneously releases hyaluronic acid on degradation, which promotes integration and maturation of the graft.<sup>38</sup>

In a prospective, nonrandomized 5-year follow-up study, patients treated with Hyalograft C had significantly better improvement in clinical IKDC subjective and objective score than patients treated with microfracture.<sup>39</sup> In a subsequent study, Kon *et al.*<sup>40</sup> confirmed these findings and reported complete filling of the cartilage defect in 26 out of 40 patients using MRI in combination with the MOCART scoring scale. They also statistically correlated their clinical findings with their MRI findings.<sup>40</sup> Similar clinical and MOCART results were reported in a 7-year follow-up case series.<sup>41</sup> In another study, Kon *et al.*<sup>42</sup> prospectively compared Hyalograft C with microfracture in 40 male professional or semiprofessional soccer players at 2 and 7.5 years postoperation. Although they reported similar percentage return to competition (average 83%) in both groups, those treated with Hyalograft C had significantly longer time to recovery but sustained better clinical results (ICRS score) than those treated with microfracture.<sup>42</sup>

Currently, Hyalograft C is being marketed in Italy and other European countries. It is not available in the United States and a search of clinicaltrials.gov yields no results.<sup>38,43</sup>

### **ChondroCelect (TiGenix, Leuven, Belgium)**

ChondroCelect (CC) is a unique cell-based cartilage repair technique that uses a procedure called characterized

chondrocyte implantation (CCI). With CCI a gene expression score is used when isolating and expanding the autologous chondrocytes in a laboratory. The ChondroCelect score was developed to predict the cells ability to form stable products, such as hyaline cartilage, necessary for cartilage growth *in vivo*.<sup>44,45</sup> However, CC has mostly been studied using the first-generation periosteal flap ACI technique.

The most recent randomized clinical trial comparing CC with microfracture was published in 2011 and consisted of 51 patients with grade III and IV lesions of the femoral condyle who were treated with CC and 61 in the microfracture arm.<sup>46</sup> These patients were followed for 5 years using the overall Knee Injury and Osteoarthritis Outcome Score (oKOOS).<sup>47</sup> Reported results showed a significant overall improvement in oKOOS scores from baseline in both arms but no significant difference in CC versus microfracture. There was a significantly better improvement in those patients treated with CCI whose symptom onset occurred less than 3 years prior to surgery. This study suggests that time since onset of symptoms is an important variable in considering CC as a treatment option. The study also looked at adverse events, which were comparable between the 2 arms. However, patients treated with CC had significantly more joint crepitation from 36 months on than the microfracture group did (9.3% for CC vs. 0% for microfracture).<sup>46</sup> An extension study expanded the sample size to 264 patients treated with CC, but this study was retrospective and not a randomized control trial compared with a standard treatment. This publication reported 89% of patients with a therapeutic effect after an average of 2.2 years of follow-up based on a clinical global impression for efficacy scale.<sup>44</sup>

Currently, CC is approved in Europe but not in the United States. The phase III clinical trial has been completed and has results as described.<sup>46</sup> However, despite some positive reported results, there are still concerns about CC. There was no significant difference between CC and microfracture outcomes and there were more complications reported with CC. These may be due to the use of first-generation ACI technique with CC but could also be due to the complexity of the CC/ACI procedure. In addition, CC is more expensive than microfracture, thus calling into question the cost-effectiveness of this procedure.

In a follow-up study, Gerlier *et al.*,<sup>48</sup> with funding from TiGenix, reported on the cost-effectiveness of CC. Based on 5-year outcomes from the phase III randomized control trial, and on literature that reported on the incidence of osteoarthritis, the need for total knee replacement, and the rate of revision, the authors established a 40-year decision tree model to compare CC with microfracture. The authors report that CC cost an additional €16,229 per quality adjusted life year as compared with microfracture, a figure which they deemed to be cost-effective if the correlation between hyaline cartilage repair tissue and the avoidance of osteoarthritis and total knee replacement could be verified in the long term.<sup>48</sup> This holds true for all autologous

chondrocyte techniques, which carry a high cost, but have the potential to alter the progression of acute articular cartilage injury to chronic joint deterioration, potentially leading to long-term cost-effectiveness.

Unfortunately, current evidence regarding CC and all the later generation ACI techniques are mostly based on clinical trials that are limited by the number of participants and follow-up time, although future research is trending toward improved study design.

## Single-Step Procedures

### Cartilage Autograft Implantation System (DePuy Mitek, Raynham, MA)

Cartilage Autograft Implantation System (CAIS) represents another type of advanced generation ACI. In a single procedure, hyaline cartilage is arthroscopically harvested from a non-weight-bearing portion of the knee followed by placement of the harvested tissue into a device that minces the cartilage into 1- to 2-mm pieces. The minced cartilage is uniformly dispersed into a biodegradable scaffold, which is made of 35% polycaprolactone and 65% polyglycolic acid reinforced with a polydioxanone mesh. The implant is then molded and implanted into the defect with the cartilage fragments facing the subchondral bone and then affixed with biodegradable staple anchors.

Recently, Cole *et al.*<sup>49</sup> reported positive results for CAIS versus microfracture in a prospective randomized control trial of 29 patients conducted at 5 different medical centers in the United States. Based on IKDC and KOOS scores, patients undergoing CAIS had significantly better results after 24 months than those patients who were treated with microfracture.<sup>49</sup> However, there was little to no significant difference in MRI qualitative analysis, and no quantitative imaging was done. Additionally, the authors acknowledged the need for second look arthroscopy or biopsy to demonstrate the growth of articular cartilage after the CAIS procedure.

Currently, a large multicentered randomized control phase III trial of CAIS versus microfracture is ongoing and recruiting patients in the United States. The estimated enrollment is 364 patients with an estimated completion date of December 2016.<sup>50</sup>

## Discussion

With our physically active, aging population, articular cartilage defects represent an increasingly prevalent and concerning problem.<sup>1,2</sup> Articular cartilage lacks the ability to regenerate because of it being avascular, aneural, alymphatic, and having low cellularity. Furthermore, chondrocytes have a low proliferation potential and their ability to respond to mechanical, chemical, and pharmacological factors decreases with age.<sup>10</sup>



As full-thickness defects in articular cartilage continue to pose a challenge to treat, new methods of repair are being researched. Although prior cartilage repair techniques have been shown to have positive results, newer methods have been developed in an attempt to eliminate the limitations of first-generation approaches, such as periosteal graft failure, delamination, and periosteal hypertrophy.<sup>16</sup> The newer techniques have been successful at eliminating these complications and there is some evidence for improved tissue quality with the newest generation techniques. However, more randomized clinical studies comparing newer generation autologous techniques with currently used standard repair methods over longer periods of time need to be conducted to demonstrate long-term tissue longevity and overall effectiveness in order to justify the cost of these newer approaches.

Since full-thickness articular cartilage defects are thought to predispose to the early onset of degenerative osteoarthritis, there is potential for the newer generation cell based cartilage repair techniques to be cost-effective in the long term. This is predicated on the reduction of the progression of osteoarthritis and the delayed need for total joint arthroplasty.<sup>10,51</sup> Thus far, there are limited data on the incremental cost-effectiveness, defined as the increased cost per unit of beneficial outcome. As research on ACI continues, the initial price of ACI as compared to the potential long-term physiological benefit and reduction of long term cost should be considered.

The products discussed in the current review differ with respect to the scaffold used. Although all are 3 dimensional, the composition of each matrix differs. Future studies should compare the scaffolds based on chondrocyte expansion and the ability to effectively integrate into the defect site and with the adjacent articular cartilage. Additionally, some products have unique culturing processes allowing for the potential to combine the beneficial aspects of different procedures. By selecting for chondrocytes with a higher rate of proliferation and metabolic activity, techniques like ChondroCelect may foster a more durable repair tissue. Current evidence compares ACI to a standard technique, mostly microfracture. Future randomized control trials should compare the techniques reviewed here with each other to demonstrate which scaffold or procedure is superior, especially in larger defects where microfracture is insufficient.

Symptomatic articular cartilage defects continue to be a complex problem for the treating orthopedic surgeon to effectively manage. During the past few years, significant progress has been made with respect to techniques for surgical repair of these lesions. Advances in tissue engineering, scaffolds and autologous chondrocyte culturing may hold promise in our quest to alter the natural history of symptomatic chondral disease. The recent development of newer generation autologous products and procedures has brought us one step closer to this goal.

## Summary

Name	FDA Clinical Trial Status (Estimated Completion) <sup>43</sup>	Three-Dimensional Matrix Description	Chondrocyte Preparation Method	Number of Procedures and Time Between Procedures	Best Outcome
BioCart II	Phase II (May 2015)	Plasminogen-free fibrinogen and thrombin with hyaluronic acid <sup>4</sup>	Autologous human serum and FGF2v1 <sup>4</sup>	2; 3-6 weeks apart	Significant improvement in clinical and T2 MRI score after 17 months <sup>8</sup>
MACI	Phase III (May 2015)	Cell-free porcine collagen I/III <sup>12</sup>	Laboratory culture (no specific protocol)	2; 4-6 weeks apart	Significantly clinical improvement vs. microfracture after 24 months <sup>18</sup>
Cartipatch	Phase III (December 2012, December 2011)	Agarose-alginate hydrogel <sup>25</sup>	Washed 3 times and cultured with culture medium supplemented with 10% autologous serum, ascorbic acid, fungicide, and antibiotic <sup>25</sup>	2; 3 weeks	2-year follow-up in 17 patients showed significant clinical improvement and 8/11 patients with histologic hyaline-like cartilage <sup>25</sup>
NeoCart	Phase III (March 2015)	Type I collagen matrix <sup>33</sup>	Cultured in high-pressure bioreactor <sup>33</sup>	2; 6-9 weeks <sup>33,34</sup>	Significantly superior to microfracture after 24 months based on clinical scores in 30 patients <sup>34</sup>

(continued)

## Summary (continued)

Name	FDA Clinical Trial Status (Estimated Completion) <sup>43</sup>	Three-Dimensional Matrix Description	Chondrocyte Preparation Method	Number of Procedures and Time Between Procedures	Best Outcome
Hyalograft-C	No ongoing clinical trial	Hyaff 11 (ester of hyaluronic acid) <sup>36</sup>	Expanded <i>in vitro</i> and cultured in scaffold <sup>36</sup>	2; 2 weeks <sup>36</sup>	Significant clinical improvement from baseline and complete filling of defect on MRI in 57% of lesions after 7-year follow-up <sup>41</sup>
ChondroCelect	Phase III published	No specific matrix. Cells cultured after gene marker profile analysis	Given score based on gene expression profile to predict ability to form hyaline cartilage <sup>45</sup>	2; 4 weeks <sup>45</sup>	89% (234/264) of patients had clinical improvement after 2.2 years <sup>44</sup>
CAIS	Phase III (December 2016)	35% polycaprolactone, 65% polyglycolic acid, reinforced with polydioxanone mesh <sup>49</sup>	Devise minces cartilage and distributes into scaffold intraoperatively <sup>49</sup>	1 (harvest and implantation during the same procedure) <sup>49</sup>	Significant improvement in clinical score vs. microfracture after 2 years <sup>49</sup>

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical Approval

This study was approved by our institutional review board.

## References

- Aroen A, Loken S, Heir S, Alvik E, Ekeland A, Granlund OG, *et al.* Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med.* 2004;32(1):211-5.
- Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy.* 1997;13(4):456-60.
- BioCart. Autologous Cartilage System. 2011; <http://www.prochon.com/products/biocart-system/>. Accessed August 6, 2011.
- Nehrer S, Chiari C, Domayer S, Barkay H, Yayon A. Results of chondrocyte implantation with a fibrin-hyaluronan matrix: a preliminary study. *Clin Orthop Relat Res.* 2008;466(8):1849-55.
- Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, *et al.* Development and validation of the international knee documentation committee subjective knee form. *Am J Sports Med.* 2001;29(5):600-13.
- Domayer SE, Welsch GH, Nehrer S, Chiari C, Dorotka R, Szomolanyi P, *et al.* T2 mapping and dGEMRIC after autologous chondrocyte implantation with a fibrin-based scaffold in the knee: preliminary results. *Eur J Radiol.* 2009;73(3):636-42.
- Marlovits S, Striessnig G, Resinger CT, Aldrian SM, Vecsei V, Imhof H, *et al.* Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging. *Eur J Radiol.* 2004;52(3):310-9.
- Eshed I, Trattnig S, Sharon M, Arbel R, Nierenberg G, Konen E, *et al.* Assessment of cartilage repair after chondrocyte transplantation with a fibrin-hyaluronan matrix: correlation of morphological MRI, biochemical T2 mapping and clinical outcome. *Eur J Radiol.* 2012;81:1216-23.
- ClinicalTrials.gov. Comparison of BioCart™ II With Microfracture for Treatment of Cartilage Defects of the Femoral Condyle. 2010; <http://www.clinicaltrials.gov/ct2/show/NCT00729716?term=biocart+II&rank=1>. Accessed January 18, 2012.
- Peretti GM, Pozzi A, Ballis R, Deponti D, Pellacci F. Current surgical options for articular cartilage repair. *Acta Neurochir Suppl.* 2011;108:213-9.
- Zheng MH, Willers C, Kirilak L, Yates P, Xu J, Wood D, *et al.* Matrix-induced autologous chondrocyte implantation (MACI): biological and histological assessment. *Tissue Eng.* 2007;13(4):737-46.
- Ventura A, Memeo A, Borgo E, Terzaghi C, Legnani C, Albisetti W. Repair of osteochondral lesions in the knee by chondrocyte implantation using the MACI(R) technique. *Knee Surg Sports Traumatol Arthrosc.* 2011;20(1):121-6.

13. Jacobi M, Villa V, Magnussen RA, Neyret P. MACI— a new era? *Sports Med Arthrosc Rehabil Ther Technol*. 2011;3(1):10.
14. Zeifang F, Oberle D, Nierhoff C, Richter W, Moradi B, Schmitt H. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation. *Am J Sports Med*. 2010;38(5):924-33.
15. Sohn DH, Lottman LM, Lum LY, Kim SG, Pedowitz RA, Coutts RD, *et al*. Effect of gravity on localization of chondrocytes implanted in cartilage defects. *Clin Orthop Relat Res*. 2002(394):254-62.
16. Wood JJ, Malek MA, Frassica FJ, Polder JA, Mohan AK, Bloom ET, *et al*. Autologous cultured chondrocytes: adverse events reported to the United States Food and Drug Administration. *J Bone Joint Surg Am*. 2006;88(3):503-7.
17. Bartlett W, Skinner JA, Gooding CR, Carrington RW, Flanagan AM, Briggs TW, *et al*. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. *J Bone Joint Surg Br*. 2005;87(5):640-5.
18. Basad E, Ishaque B, Bachmann G, Sturz 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(4):519-27.
19. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res*. 1985(198): 43-9.
20. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med*. 1982;10(3):150-4.
21. ICRS CIEP. The International Cartilage Repair Society Web site. 2000; [http://www.cartilage.org/\\_files/contentmanagement/ICRS\\_evaluation.pdf](http://www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf). Accessed January 25, 2012.
22. Genzyme. News: Genzyme Introduces Unique, Novel Technology to Further Demonstrate Quality of its Cartilage Repair Products. 2007; <http://www.maci.com/patient/news/press-release-nov2007.aspx>. Accessed January 26, 2012.
23. Sanofi. Sanofi Biosurgery Product MACI Demonstrates Statistically Significant Clinical Outcomes Compared to Microfracture 2012; <http://sanofi.mediaroom.com/index.php?s=43&item=366>. Accessed July 18, 2012.
24. Clinicaltrials.gov. Extension Study for Patients Who Completed Previous Study MACI00206 [NCT00719576] of MACI® Implant for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle. 2011; <http://www.clinicaltrials.gov/ct2/show/NCT01251588?term=maci&rank=1>. Accessed January 26, 2012.
25. Selmi TA, Verdonk P, Chambat P, Dubrana F, Potel JF, Barnouin L, *et al*. Autologous chondrocyte implantation in a novel alginate-agarose hydrogel: outcome at two years. *J Bone Joint Surg Br*. 2008;90(5):597-604.
26. TBF. Cartipatch Service. [http://www.tbf-lab.com/ortho/index.php?option=com\\_content&view=article&id=80&Itemid=82&lang=en](http://www.tbf-lab.com/ortho/index.php?option=com_content&view=article&id=80&Itemid=82&lang=en). Accessed January 26, 2012.
27. Mainil-Varlet P, Aigner T, Brittberg M, Bullough P, Hollander A, Hunziker E, *et al*. Histological assessment of cartilage repair: a report by the Histology Endpoint Committee of the International Cartilage Repair Society (ICRS). *J Bone Joint Surg Am*. 2003;85(Suppl 2):45-57.
28. O'Driscoll SW, Marx RG, Beaton DE, Miura Y, Gallay SH, Fitzsimmons JS. Validation of a simple histological-histochemical cartilage scoring system. *Tissue Eng*. 2001; 7(3):313-20.
29. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. *Eur J Radiol*. 2006;57(1):16-23.
30. ClinicalTrials.gov. Comparison of autologous chondrocyte implantation versus mosaicplasty: a randomized trial (Cartipatch). 2010; <http://www.clinicaltrials.gov/ct2/show/NCT00560664?term=cartipatch&rank=1>. Accessed January 26, 2010.
31. ClinicalTrials.gov. Comparison of microfracture treatment and CARTIPATCH® Chondrocyte graft treatment in femoral condyle lesions. 2010; <http://clinicaltrials.gov/ct2/show/NCT00945399?term=cartipatch&rank=2>. Accessed February 28, 2012.
32. Histogenics. NeoCart. 2012; <http://www.histogenics.com/contact/>. Accessed January 27, 2012.
33. Crawford DC, Heveran CM, Cannon WD, Jr, Foo LF, Potter HG. An autologous cartilage tissue implant NeoCart for treatment of grade III chondral injury to the distal femur: prospective clinical safety trial at 2 years. *Am J Sports Med*. 2009;37(7):1334-43.
34. Crawford DC, DeBerardino TM, Williams RJ, 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. *J Bone Joint Surg Am*. 2012;94(11):979-89.
35. ClinicalTrials.gov. NeoCart phase 2 clinical trial. 2010; <http://www.clinicaltrials.gov/ct2/show/NCT00548119?term=neocart&rank=1>. Accessed January 27, 2012.
36. Marcacci M, Berruto M, Brocchetta D, Delcogliano A, Ghinelli D, Gobbi A, *et al*. Articular cartilage engineering with Hyalograft C: 3-year clinical results. *Clin Orthop Relat Res*. 2005(435):96-105.
37. Grigolo B, Lisignoli G, Piacentini A, Fiorini M, Gobbi P, Mazzotti G, *et al*. Evidence for redifferentiation of human chondrocytes grown on a hyaluronan-based biomaterial (HYAff 11): molecular, immunohistochemical and ultrastructural analysis. *Biomaterials*. 2002;23(4):1187-95.
38. Anika. Hyalograft C Autograft. <http://www.anikatherapeutics.com/products/Orthobiologics/hyalograft.html>. Accessed February 1, 2012.
39. Kon E, Gobbi A, Filardo G, Delcogliano M, Zaffagnini S, Marcacci M. Arthroscopic second-generation autologous

- chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years. *Am J Sports Med.* 2009;37(1):33-41.
40. Kon E, Di Martino A, Filardo G, Tetta C, Busacca M, Iacono F, *et al.* Second-generation autologous chondrocyte transplantation: MRI findings and clinical correlations at a minimum 5-year follow-up. *Eur J Radiol.* 2010;79(3):382-8.
  41. Filardo G, Kon E, Di Martino A, Iacono F, Marcacci M. Arthroscopic second-generation autologous chondrocyte implantation: a prospective 7-year follow-up study. *Am J Sports Med.* 2011;39(10):2153-60.
  42. Kon E, Filardo G, Berruto M, Benazzo F, Zanon G, Della Villa S, *et al.* Articular cartilage treatment in high-level male soccer players: a prospective comparative study of arthroscopic second-generation autologous chondrocyte implantation versus microfracture. *Am J Sports Med.* 2011;39(12):2549-57.
  43. ClinicalTrials.gov. ClinicalTrials.gov. 2012; <http://www.clinicaltrials.gov/>. Accessed February 1, 2012.
  44. Vanlauwe J, Huylebroeck J, Van Der Bauwhede J, Saris D, Veeckman G, Bobic V, *et al.* Clinical outcomes of characterized chondrocyte implantation. *Cartilage.* 2012;3(2):173-80.
  45. Saris DB, Vanlauwe J, Victor J, Haspl M, Bohnsack M, Fortems Y, *et al.* Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. *Am J Sports Med.* 2008;36(2):235-46.
  46. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP. 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(12):2566-74.
  47. Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis Cartilage.* 2009;17(11):1434-9.
  48. Gerlier L, Lamotte M, Wille M, Kreuz PC, Vanlauwe J, Dubois D, *et al.* The cost utility of autologous chondrocytes implantation using ChondroCelect(R) in symptomatic knee cartilage lesions in Belgium. *Pharmacoeconomics.* 2012;28(12):1129-46.
  49. Cole BJ, Farr J, Winalski CS, Hosea T, Richmond J, Mandelbaum B, *et al.* Outcomes after a single-stage procedure for cell-based cartilage repair: a prospective clinical safety trial with 2-year follow-up. *Am J Sports Med.* 2011;39(6):1170-9.
  50. ClinicalTrials.gov. Cartilage Autograft Implantation System (CAIS) for the repair of knee cartilage through cartilage regeneration. 2012; <http://www.clinicaltrials.gov/ct2/show/NCT00881023?term=cais&rank=1>. Accessed February 14, 2012.
  51. Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al.* Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technol Assess.* 2005;9(47):iii-iv, ix-x, 1-82.