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Autologous Chondrocyte Implantation

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Policy History

Last Review
05/01/2025
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Next Review: 02/26/2026

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Policy

Scope of Policy

This Clinical Policy Bulletin addresses autologous chondrocyte implantation.

I. Medical Necessity

Aetna considers autologous chondrocyte implants medically necessary for repairing cartilage defects of the knee in members who have symptoms of disabling knee pain related to a full thickness, focal chondral defect with all of the following:

A. Age 15 years or older with documented growth plate closure, or adults less than 55 years of age; *and*
B. Body mass index (BMI) less than or equal to 35 (see Appendix); *and*
C. Cooperative person for post-operative weight bearing restrictions and activity restrictions together with a potential for completion of post-operative rehabilitation; *and*
D. Failure of conservative therapy (minimum of 6 weeks of physical therapy in the past year); *and*
E. Focal articular cartilage defect down to but not through the subchondral bone on a load bearing surface of the femoral condyle (medial, lateral, trochlear) or the patella) (i.e., grade IV chondral defect); *and*
F. The opposing articular surface should be generally free of disease or injury; *and*
G. Informed consent with realistic expectations; *and*
H. No active inflammatory or other arthritis, clinically and by X-ray; *and*
I. Presence of disabling pain and/or knee locking which limits activities of daily living; *and*
J. Procedure is not being done for treatment of degenerative arthritis (osteoarthritis); *and*
K. Size of defect measures less than 7 mm in depth, less than 6.0 cm in length, and area ranging from 1.6 to 10 square cm; *and*
L. Stable and aligned knee with intact meniscus and normal joint space on X-ray (a corrective procedure in combination with, or prior to, chondrocyte implantation may be necessary to ensure stability, alignment and normal weight distribution within the joint).

Aetna considers FDA-approved matrix-induced chondrocyte implantation (e.g., MACI (Vericel) autologous cultured chondrocytes on porcine collagen membrane) an equally acceptable alternative to autologous cultured chondrocytes (e.g., Carticel) for the medically necessary indications for autologous chondrocyte implants listed above. Note: In 2017, Carticel was replaced with MACI and is no longer marketed in the United States (Vericel, 2018).

II. Experimental, Investigational, or Unproven

Aetna considers the following experimental, investigational, or unproven because of insufficient evidence of safety and effectiveness:

A. Autologous chondrocyte implants for the following:

1. Ankle (talar) lesions, or lesions of other joints (e.g., hip and shoulder); *or*
2. Individuals who have had a previous total meniscectomy; *or*
3. Individuals with a cartilaginous defect associated with osteoarthritis, rheumatoid arthritis or inflammatory diseases or where an osteoarthritic or inflammatory process significantly and adversely affects the quality of the peri lesional cartilage; *or*
4. Individuals with known history of anaphylaxis to gentamicin or sensitivities to materials of bovine origin; *or*
5. Initial or first line of surgical therapy;

B. Autologous matrix-induced chondrogenesis (AMIC) for articular cartilage defects of the talus, patella-femoral lesions and other osteochondral defects / lesions;

C. Autologous platelet-rich plasma and fibrin-augmented minced cartilage implantation for the treatment of chondral lesions of the knee;

D. Combined meniscal allograft and autologous chondrocyte implantation of the knee;

E. Combination of autologous chondrocyte implantation and osteochondral autograft transfer system for surgical repair of cartilage defects of the knee;

F. Combined autologous chondrocyte implantation and meniscus reconstruction for large chondral defects due to discoid lateral meniscus tears;

G. Combined autologous chondrocyte implantation and osteochondral autograft transfer for large knee osteochondral lesions;

H. Hydrogel-enhanced autologous chondrocyte implantation for cartilage repair;

I. Microfracture- and xeno-matrix-induced chondrogenesis for the treatment of focal traumatic cartilage defects of the knee;
J. Two-stage bone and meniscus allograft and autologous chondrocytes implant for the treatment of unicompartmental osteoarthritis of the knee.

III. Related CMS Coverage Guidance

This Clinical Policy Bulletin (CPB) supplements but does not replace, modify, or supersede existing Medicare Regulations or applicable National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs). The supplemental medical necessity criteria in this CPB further define those indications for services that are proven safe and effective where those indications are not fully established in applicable NCDs and LCDs. These supplemental medical necessity criteria are based upon evidence-based guidelines and clinical studies in the peer-reviewed published medical literature. The background section of this CPB includes an explanation of the rationale that supports adoption of the medical necessity criteria and a summary of evidence that was considered during the development of the CPB; the reference section includes a list of the sources of such evidence. While there is a possible risk of reduced or delayed care with any coverage criteria, Aetna believes that the benefits of these criteria – ensuring patients receive services that are appropriate, safe, and effective – substantially outweigh any clinical harms.

Code of Federal Regulations (CFR): 42 CFR 417; 42 CFR 422; 42 CFR 423.

Internet-Only Manual (IOM) Citations: CMS IOM Publication 100-02, Medicare Benefit Policy Manual; CMS IOM Publication 100-03 Medicare National Coverage Determination Manual.

Medicare Coverage Determinations: Centers for Medicare & Medicaid Services (CMS), Medicare Coverage Database [Internet]. Baltimore, MD: CMS; updated periodically. Available at: Medicare Coverage Center

(https://www.cms.gov/medicare/coverage/center?redirect=/center/coverage.asp). Accessed November 7, 2023.

IV. Related Policies

- CPB 0637 - Osteochondral Autografts (Mosaicplasty, OATS) (../600_699/0637.html)

CPT Codes / HCPCS Codes / ICD-10 Codes

Autologous chondrocyte implantation:

Code	Code Description
CPT codes covered if selection criteria are met:	
27412	Autologous chondrocyte implantation, knee
29870	Arthroscopy, knee, diagnostic; with or without synovial biopsy (separate procedure)
Other CPT codes related to the CPB:	
27416	Osteochondral autograft(s), knee, open (eg, mosaicplasty) (includes harvesting of autograft[s]) [not covered in combination with autologous chondrocyte implantation]
27447	Arthroplasty, knee, condyle and plateau; medial AND lateral compartments with or without patella resurfacing (total knee arthroplasty)
29866	Arthroscopy, knee, surgical; implantation of osteochondral autograft(s) (e.g., mosaicplasty) (includes harvesting of autografts) [not covered in combination with autologous chondrocyte implantation]
29871	Arthroscopy, knee, surgical; for infection, lavage and drainage
29874	for removal of loose body or foreign body (e.g., osteochondritis dissecans fragmentation, chondral fragmentation)
29877	debridement/shaving of articular cartilage (chondroplasty)

Code	Code Description
29879	abrasion arthroplasty (includes chondroplasty where necessary) or multiple drilling or microfracture
HCPCS codes covered if selection criteria are met:	
J7330	Autologous cultured chondrocytes, implant
S2112	Arthroscopy, knee, surgical, for harvesting of cartilage (chondrocyte cells)
ICD-10 codes covered if selection criteria are met (not all-inclusive):	
M23.000 - M23.92	Internal derangement of knee
M25.161 - M25.169	Fistula, knee
M25.261 - M25.269	Flail joint, knee
M25.361 - M25.369	Other instability, knee
M25.561 - M25.569	Pain in knee
M25.861 - M25.869	Other specified joint disorders, knee
M89.155 - M89.158	Physeal arrest, distal femur
M89.160 - M89.163	Physeal arrest, proximal tibia
Z68.1 - Z68.35	Body Mass Index less than 19, adult - 35.9 [BMI less than or equal to 35]
Numerous options	Injury, knee, leg, ankle, and foot [Codes not listed due to expanded specificity]
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
M00.00 - M02.9	Infectious arthropathies
M05.00 - M19.93	Inflammatory polyarthropathies and osteoarthritis

Code	Code Description
M24.00 - M24.9	Other specific joint derangements
Z68.36 - Z68.45	Body Mass Index 36.0 - 70+, adult
Z87.892	Personal history of anaphylaxis [to gentamicin]
Z88.8	Allergy status to other drugs, medicaments and biological substances status [materials of bovine origin]
Combination Meniscal Allograft and Autologous Chondrocyte implantation:	
CPT codes not covered for indications listed in the CPB:	
27412	Autologous chondrocyte implantation, knee
29868	Arthroscopy, knee, surgical; meniscal transplantation (includes arthrotomy for meniscal insertion), medial or lateral
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
M94.8x8	Other specified disorders of cartilage, other site [For large knee osteochondral lesion]
M23.241 - M23.249	Derangement of anterior horn of lateral meniscus due to old tear or injury
M23.251 - M23.259	Derangement of posterior horn of lateral meniscus due to old tear or injury
M23.261 - M23.269	Derangement of other lateral meniscus due to old tear or injury
S83.251A - S83.259S	Bucket-handle tear of lateral meniscus, current injury
S83.261A - S83.269S	Peripheral tear of lateral meniscus, current injury
S83.271A - S83.271S	Complex tear of lateral meniscus, current injury
S83.281A - S83.289S	Other tear of lateral meniscus, current injury
Autologous matrix-induced chondrogenesis (AMIC):	
CPT codes not covered for indications listed in the CPB:	
Autologous matrix-induced chondrogenesis (AMIC) - no specific code	

Code	Code Description
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
M22.2x1 – M22.2x9	Patellofemoral disorders [patella-femoral lesions]
M24.10	Other articular cartilage disorders, unspecified site [for articular cartilage defects of the talus]
M24.171	Other articular cartilage disorders, right ankle [for articular cartilage defects of the talus]
M24.172	Other articular cartilage disorders, left ankle [for articular cartilage defects of the talus]
M24.173	Other articular cartilage disorders, unspecified ankle [for articular cartilage defects of the talus]
Combination 2-stage bone and Meniscal Allograft and Autologous Chondrocyte implantation:	
CPT codes not covered for indications listed in the CPB:	
20900	Bone graft, any donor area; minor or small (eg, dowel or button)
20902	Bone graft, any donor area; major or large
27412	Autologous chondrocyte implantation, knee
29868	Arthroscopy, knee, surgical; meniscal transplantation (includes arthrotomy for meniscal insertion), medial or lateral
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
M17.0 - M17.9	Osteoarthritis of knee
Microfracture, and xeno-matrix induced chondrogenesis:	
CPT codes not covered for indications listed in the CPB:	
Microfracture, and xeno-matrix induced chondrogenesis- no specific code	
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
S83.30XA - S83.32XS	Tear of articular cartilage of knee, current [Focal traumatic cartilage defects of knee]

Background

Articular cartilage damaged through acute or chronic trauma or osteochondritis dessecans, has limited ability to regenerate, leading to the symptoms of pain, restricted mobility and locking. Current treatment methods to stimulate repair of the cartilage include shaving the margins of the damaged cartilage to remove mechanical obstructions or irritants (abrasion or debridement) or drilling through the cartilage through the underlying bone into the vascular marrow in order to permit the ingrowth of fibrocartilage from the marrow. Long-standing severe damage to the articular cartilage can lead to debilitating osteoarthritis, which ultimately may require a total knee arthroplasty.

Autologous chondrocyte implants (autologous chondrocyte transplant) (Carticel, Genzyme Inc., Cambridge, MA) has been investigated as a means of a 3-step treatment for repairing cartilage defects in the knee. First, normal cartilage is harvested from a joint margin during an arthroscopic biopsy procedure. This biopsy of an articular surface serves as the source of cultured chondrocytes. This specimen of live articular cartilage is placed into a culture medium. Under a strictly controlled environment the cells are separated from the cartilage. These cells are then multiplied using a cell-culture technique. They are stored in the frozen state and are thawed and have a final culturing process before they are shipped to the operating room on the day of the implantation. It takes about 6 weeks to culture chondrocytes for implantation. Approximately 12 million cartilage cells are present in the 0.4ml medium that is ultimately implanted into the defect. The cultured chondrocytes are implanted into the cartilage defect in a second open arthrotomy procedure.

Patients are referred for autologous chondrocyte implantation after already having had surgery for an articular cartilage problem. If the patient remains symptomatic, and the patient and the surgeon decide that autologous chondrocyte implant is the best option, then an arthroscopic biopsy is planned.

Ideally, candidates for autologous chondrocyte implant should be between 15 and 60 years of age, have full thickness localized defects of the femoral condyles, have intact menisci, have no generalized

chondromalacia, have no limb mis-alignment and are willing and able to undergo vigorous rehabilitation. This procedure is not recommended for patients who have an unstable knee and for patients sensitive to materials of bovine origins. It is also not recommended for use in children, and not yet in any joint other than the knee.

There is a paucity of evidence on the comparative efficacy of autologous chondrocyte implants to established surgical procedures for articular cartilage defects. An assessment by the BlueCross BlueShield Association Technology Evaluation Center (TEC, 2003) stated that there was insufficient evidence that the unique components of autologous chondrocyte implantation -- the implantation of cultured chondrocytes -- improves clinical outcomes. The TEC assessment noted that autologous chondrocyte implantation has 4 components -- (i) debridement of the injured area, (ii) coverage of the injured area with a periosteal tissue flap, (iii) implantation of cultured chondrocytes, and (iv) physical rehabilitation. The TEC assessment noted that 3 of the 4 components of autologous chondrocyte implantation -- use of a periosteal flap, debridement and rehabilitation – are not unique to autologous chondrocyte implantation, and these components of the procedure may account for some or all of the clinical improvements noted in uncontrolled studies of this procedure. The TEC assessment stated: "[t]he available evidence is not sufficient to permit conclusions about the independent effect of the novel components of [autologous chondrocyte transplantation] ACT on health outcomes. The available evidence reports that ACT for the treatment of clinically significant, focal defects of the femoral condyle is associated with improved health outcomes such as diminished pain and improved joint function over the short term. However, the available evidence is not sufficient to determine if the improvements are caused by the use of autologous chondrocytes (the defining feature of ACT) or how the outcomes achieved with ACT compare with the outcomes achievable simply by use of debridement with rehabilitation."

The main deficiency of the existing evidence is that there are no published controlled studies that actually compare the outcomes of ACT with any other treatments or even with the natural progression of the disease. The available studies do report the proportions of patients

treated with ACT who achieved various levels of outcomes, but there is no way to determine if those outcomes are better than, the same as, or worse than, the outcomes that would have occurred with other treatments.

Other published structured evidence reviews have reached similar conclusions about the paucity of comparative studies of autologous chondrocyte implantation (ACI). The National Institute for Clinical Excellence (2005) reviewed the evidence supporting the use of autologous chondrocyte implantation for full-thickness cartilage defects in knee joints. The assessment noted the paucity of prospective controlled clinical studies comparing the outcomes of autologous chondrocyte implantation to alternative treatment modalities. The assessment noted that most of the available evidence for autologous chondrocyte implant is from uncontrolled case series, and that this literature is subject to bias because of the inherent weakness of case series. The assessment also noted that the long-term impact of autologous chondrocyte implantation is poorly documented. The assessment concluded that it is not possible to draw definitive conclusions about the clinical effectiveness of this technology based on available literature. Quality Improvement Scotland (NHS QIS, 2005) concurred with the conclusions of the NICE assessment.

A evidence review prepared for the Cochrane Collaboration by Wasiak et al (2006) concluded that "[t]he use of ACI and other chondral resurfacing techniques is becoming increasingly widespread. However, there is at present no evidence of significant difference between ACI and other interventions." Four randomized controlled trials including 266 participants met inclusion criteria. One trial of ACI versus mosaicplasty (Bentley et al, 2003) reported statistically significant results for ACI at 1 year, but only in a post-hoc subgroup analysis of participants with medial condylar defects; when taking into account all participants, no significant differences were noted. A second trial of ACI versus mosaicplasty found no statistically significant difference in clinical outcomes at 2 years (Horas et al, 2003). There was no statistically significant difference in outcomes at 2 years in a trial comparing ACI with microfracture (Knutsen et al, 2004). In addition, 1 trial of matrix-guided ACI (MACI) versus microfracture did not contain enough long-term results to reach definitive conclusions (Basad et al, 2004). The review concluded that "[a]dditional

good quality randomised controlled trials with long-term functional outcomes are required." An updated Cochrane review reached similar conclusions, stating that "[t]here is insufficient evidence to draw conclusions on the use of ACI for treating full thickness articular cartilage defects in the knee. Further good quality randomised controlled trials with long-term functional outcomes are required."

An assessment by the National Coordinating Centre for Health Technology Assessment (NCCHTA) (Jobanputra et al, 2001) concluded that "autologous chondrocyte transplantation should be regarded as an experimental therapy." More recently, a cost-effectiveness analysis from NCCHTA (Clar et al, 2005) concluded that "[t]here is insufficient evidence at present to say that ACI is cost-effective compared with microfracture or mosaicplasty."

An assessment of autologous chondrocyte transplantation by the French National Authority for Health (HAS, 2005) concluded: "It is difficult to determine either the benefit/risk ratio or the role of the technique in managing isolated chondral tissue defects in young subjects, as there are insufficient comparative trials of a good level of evidence or long-term follow-up. Autologous chondrocyte transplantation is an emerging technique which is still very much in the development stage."

A systematic evidence review of autologous chondrocyte transplantation by the Galacian Agency for Health Technology Assessment (AVALIA-T, 2005) found that "[t]here is no evidence showing that ACI is better than other procedures on the treatment of chondral lesions of the knee." A reassessment of ACI by the Galacian Agency for Health Technology Assessment (AVALIA-T, 2006) reached similar conclusions: "Most of the articles are poor-quality case series; and cohort studies do not improve existing evidence. Clinical trials do not suggest better outcomes when comparing ACI against other procedures (mosaicplasty); but they point MACI [matrix-guided ACI] to be safer than ACI, mainly due to a decrease on the risk of periosteal hypertrophy." The assessment concluded that ACI has yet to be proven superior to other procedures for osteochondral lesions of the knee, and that randomized controlled clinical trials of ACI and MACI of the knee and ankle are needed.

A systematic evidence review of ACI and MACI by the Ludwig Boltzmann Institute for Health Technology Assessment (LBIHTA) concluded that MACI and ACI should be considered as experimental techniques (Kunzl et al, 2009). The systematic evidence review identified controlled clinical studies of at least 20 patients and follow-up of at least 1 year. The systematic evidence review identified 9 comparative clinical trials that met inclusion criteria and 6 systematic reviews. Among these studies, a total of 566 patients were treated with mosaicplasty versus ACI, microfracture versus ACI, and ACI versus ACI. The authors said that the results of their systematic evidence review shows consistency and confirms the conclusions of earlier systematic evidence reviews. The authors found that there is no evidence that ACI or MACI leads to better outcomes in the treatment of osteochondral lesions than any of the alternative treatments, and that ACI is not superior, and is at best equal, at is much higher cost. The authors stated that the short term (1 to 2 years) and mid-term (5 years) non-inferiority in highly selected active patients is proven; however, long-term data are lacking. The authors concluded that "(M)ACI methods must be considered -- though often applied -- as experimental techniques. The risks of cultivated chondrocyts cannot be ignored, and have to be seen as a risk."

An assessment of autologous chondrocyte implanation and matrix-induced autologous chondrocyte implantation by the Australian Medical Services Advisory Committee (2010) found that, overall, the safety, and, in the short to medium term, the effectiveness of MACI/ACI appears to be comparable to those comparator procedures evaluated in the MSAC assessment. The assessment stated that the available studies were heterogeneous in terms of the patients recruited, the MACI/ACI technique used and the measures used to assess patient outcomes, which made it difficult to draw direct comparisons between the different procedures across studies. The assessment stated that a further limitation of the included studies was the length of follow-up reported. The assessment noted that it has been suggested that any differences in outcome based on formation of articular rather than fibrocartilage in the defect may be subtle and may only reveal themselves after many years of follow-up (five to 10 years). However the majority of studies in this assessment reported short to medium-term (one to three years) follow-up of patients.

Published controlled clinical trials have compared autologous chondrocyte implant to established procedures. Although results of available clinical studies have not been consistent, the strongest available evidence suggests that outcomes of microfracture may be superior to autologous chondrocyte implant. Knutsen et al (2004) compared short-term clinical outcomes of autologous chondrocyte implantation and microfracture in a randomized controlled clinical trial involving 80 persons with a single large symptomatic cartilage defect on the femoral condyle. At 2-year follow-up, these investigators reported significantly better improvement in functional status (according to the 36-item Short Form Health Survey Questionnaire (SF-36) physical component score) in the microfracture group than in the autologous chondrocyte implantation group. Knutsen et al (2007) reported on the results of 5-year follow-up. The investigators found no significant difference in the clinical and radiographic results between the ACI group and the microfracture group. At the 5-year follow-up interval, there were 9 failures (23 %) in both groups.

A study reported in abstract form by Anderson et al (2003) compared autologous chondrocyte implantation with microfracture in 46 patients with full-thickness cartilage lesions greater than 2-cm in size. The investigators reported a mean improvement in the Cincinnati score was 3.1 for autologous chondrocyte implantation and 1.3 for microfracture. The investigators reported that the reduction in pain was also better with autologous chondrocyte implantation compared with microfracture. Although this study was prospective, there was no random assignment to treatment groups; thus this study is of weaker design than the previously reported studies by Knutsen et al (2004, 2007). In addition, this study has been criticized for having a high percentage of worker's compensation patients, and 5 of the 23 patients treated with microfracture were lost to follow-up.

There is inadequate evidence that the prior performance of marrow stimulation techniques affect the outcome of subsequent autologous chondrocyte implantation. Evidence from the Study of Treatment of Articular Repair (STAR) clinical trial found no significant difference in outcome of ACI between subjects whose prior surgery had been a marrow stimulation technique and subjects whose prior surgery had been a debridement. In this multi-center clinical study, 154 patients with failed

treatment for articular cartilage defects of the knee received autologous chondrocyte implantation and were followed for 4 years. Outcomes included change from baseline in knee function, knee pain, quality of life, and overall health. The investigators reported that 126 patients (82 %) completed the protocol; 76 % of patients were treatment successes at study end, while 24 % were deemed treatment failures. Mean improvements were observed from baseline to all time points for all outcome measures. The investigators reported that results did not differ between patients whose primary surgery had been a marrow-stimulating procedure and those whose primary procedure had been a debridement alone.

Minas et al (2009) reported on a single institution study of 321 consecutive patients treated with autologous chondrocyte implantation for full-thickness cartilage defects that reached more than 2 years of follow-up. Patients were grouped based on whether they had undergone prior treatment with a marrow stimulation technique. Outcomes were classified as complete failure if more than 25 % of a grafted defect area had to be removed in later procedures because of persistent symptoms. The investigators reported that there were 522 defects in 321 patients (325 joints) treated with autologous chondrocyte implantation. On average, there were 1.7 lesions per patient. Of these joints, 111 had previously undergone surgery that penetrated the subchondral bone; 214 joints had no prior treatment that affected the subchondral bone and served as controls. Within the marrow stimulation group, there were 29 (26 %) failures, compared with 17 (8 %) failures in the control group.

Both of these studies are limited by their cohort nature. In addition, the study by Minas et al (2009) is subject to bias as all of the ACIs were treated by a single investigator, and the investigator's assessments and subsequent treatment decisions may have been influenced by the investigator's knowledge of the patients' prior procedures. Randomized controlled clinical trials are needed to better assess whether marrow-stimulation techniques reduce the likelihood of success of subsequent ACI, or whether patients who fail marrow stimulation techniques would be more likely to fail ACI regardless of whether they had a prior marrow stimulation.

Two controlled clinical trials comparing autologous chondrocyte implantation with osteochondral transplant procedures have been published in recent years, with inconsistent results. Bentley et al (2003) reported on the results of a randomized controlled clinical trial comparing autologous chondrocyte implantation to mosaicplasty in 100 patients with symptomatic defects of the articular cartilage of the knee. After a mean follow-up of 19 months, functional assessment using the modified Cincinnati and Stanmore scores and objective clinical assessment showed that 88 % had excellent or good results after autologous chondrocyte implantation compared with 69 % after mosaicplasty. Horas et al (2003) reported on the results of a randomized clinical study comparing transplantation of an osteochondral cylinder to autologous chondrocyte implantation in 40 patients with an articular cartilage lesion of the femoral condyle. The investigators reported that the improvements in function in subjects receiving autologous chondrocyte implantation lagged behind subjects receiving osteochondral cylinder transplantation. In addition, the investigators reported that the defects treated with autologous chondrocyte implantation were primarily filled with fibrocartilage rather than hyaline cartilage. These studies have been criticized for the short duration of follow-up. LaPrade (2003) commented that "[f]urther study with a minimum follow-up of 5 years as well as a complete and thorough histologic analysis is needed to determine which technique, [autologous chondrocyte implantation] or autogenous osteocartilaginous transfer, is best."

ACI for Patellar Lesions

There are no adequate prospective clinical studies of the effectiveness of autologous chondrocyte implantation on defects of the patella or talus. Prospective, randomized clinical studies are needed to assess the impact on functional status, disability, and pain. In addition, studies need to compare the effectiveness of autologous chondrocyte implantation to established methods of treatment of patellar or talus defects.

Mont et al (1999) reported on the use of autologous chondrocyte implantation for indications not supported by adequate clinical data, including the use of autologous chondrocyte implantation for patellar lesions. The investigators concluded: "The results of this study underscore the importance of controlled, application-limited experience

before the release of new procedures for widespread clinical applications. The uncontrolled use of this procedure may negatively skew the overall results for this technique, prejudicing a procedure that may be successful for the correct indications."

Noyes et al (2013) examined if there is an ideal operation for large symptomatic articular cartilage lesions on the undersurface of the patella in young patients. A systematic search of PubMed was conducted to determine the outcome of operations performed for large patellar lesions in young patients. Inclusionary criteria were English language, original clinical trials published from 1992 to 2012, patellar lesions 4 cm(2) or larger, mean patient age 50 years or younger, and all evidence levels. Of 991 articles identified, 18 met the inclusionary criteria, totaling 840 knees in 828 patients. These included 613 knees that underwent ACI (11 studies), 193 knees that had patello-femoral arthroplasty (PFA) (5 studies), and 34 knees that underwent osteochondral allografting (OA) (2 studies). The mean patient age was 37.2 years and the mean follow-up was 6.2 years. Long-term follow-up (greater than 10 years) was available in only 4 studies (2 PFA, 1 ACI, 1 OA). All studies except 1 were Level IV and none was randomized or had a control group. Twenty-one outcome instruments were used to determine knee function. When taking into account knees that either failed or had fair/poor function, the percentage of patients who failed to achieve a benefit averaged 22 % after PFA and 53 % after OA and ranged from 8 % to 60 % after ACI. In addition, all 3 procedures had unacceptable complication and re-operation rates. The authors concluded that the combination of failure rates and fair/poor results indicated that all 3 procedures had unpredictable results. They stated that a long-term beneficial effect might not occur in 1 of 3 ACI and PFA procedures and in 2 of 3 OA procedures. These researchers were unable to determine an ideal surgical procedure to treat large symptomatic patellar lesions in patients 50 years or younger.

Mandelbaum et al (2007) stated that the treatment of trochlear cartilage lesions is challenging given the likely presence of other patellofemoral joint pathologies, the topography of the area, and the limited available treatment options. Only 1 other study has examined the effectiveness of ACI for lesions of the patellofemoral joint. These researchers hypothesized that patients treated with ACI for moderate-to-large isolated lesions located on the trochlea will report improvement in the modified

overall condition scale score of the Cincinnati Knee Rating System at a minimum 2-year follow-up. Using modified scales of the Cincinnati Knee Rating System, a total of 40 Cartilage Repair Registry patients rated their overall condition and symptoms at baseline and at a mean follow-up of 59 +/- 18 months were studied. Factors likely to affect outcomes also were analyzed. At baseline, patients were between the age of 16 to 48 years, had a mean total defect size of 4.5 cm(2), and reported an overall condition score of 3.1 points (poor). Many failed a prior marrow-stimulation procedure (48 %). Other procedures performed before baseline included tibio-femoral osteotomy in 23 % and lateral release or Fulkerson for patella mal-tracking in 13 %. A total of 43 % of the patients were receiving workers' compensation at baseline. Patients reported statistically significant improvement in their mean overall condition (3.1 points pre-operatively to 6.4 points post-operatively), pain (2.6 to 6.2 points), and swelling (3.9 to 6.3 points) scores. Eleven patients experienced 17 subsequent procedures, and no patients had a failed implantation. The authors concluded that ACI appears to improve function and reduce symptoms in young-to-middle aged patients with symptomatic, full-thickness articular cartilage lesions of the trochlea.

Farr (2007) noted that many patients with patellofemoral pain have multiple knee disorders, such as chondral defects, mal-alignment, and ligament insufficiency. This investigator reviewed a treatment approach that included ACI and biomechanical altering procedures to reduce impairment and symptoms in patients with patello-femoral lesions and biomechanical disorders. Thirty-eight patients (39 knees; mean age of 31.2 years) had large isolated (trochlear, 4.3 cm2; patellar, 5.4 cm2) or bipolar (mean total surface area of 8.8 cm2) patello-femoral lesions. The minimum follow-up was 0.5 years (median of 3.1 years; range of 0.5 to 5.1 years). The author observed a median improvement for the following patient and physician scores: modified Cincinnati Knee Rating System scores (3 points each), Lysholm score (31 points), and visual analog scale scores for resting (2 points) and maximum pain (3 points). At a mean follow-up of 1.2 years in the 22 patients (23 knees) undergoing second-look arthroscopy, ACI-repaired tissue scored a median of 11 of 12 points using the International Cartilage Repair Society cartilage repair assessment. Twenty-five patients had 32 subsequent surgeries, including 14 to remove hardware from a prior osteotomy; ACI failed in 3 patients. The authors stated that despite the high rate of re-operation,

the data suggested that combined treatment of ACI and biomechanical altering procedures may be a reasonable option for selected patients with co-existing patello-femoral lesions and mechanical disorders. This was a small study (n = 38) with short-term follow-up (mean of 1.2 years); it provided Level IV evidence.

The authors noted that “a weakness of the study is that concomitant procedures do in fact complicate data interpretation. This is a reality of advanced cartilage restorations; many patients have complex problems. As this is the first peer reviewed reported series of ACI in conjunction with MAT, we reasoned that a larger inclusive series would promote more discussion than the much more limited subseries of isolated MAT/ACI (noting that there is a suggested statistical trend that there was no difference in isolated versus concomitant surgery patients). To follow a statistically powered series of isolated concomitant MAT and ACI patients over time will likely require a multicenter approach. The study design in that setting could potentially require a staged approach for other knee injuries (e.g., performing ACL reconstruction and tibial osteotomy before ACI and MAT) or address this issue with a much larger patient population to allow subgroup statistical evaluation …. Another recognized weakness of the current study is the lack of reporting of radiographic measurement of joint space. However, this was not the focus of the study; rather, the outcome measurements were patient satisfaction and function after the procedure. To allow statistical comment on radiographic measurement of joint space, it would be necessary to position/align the knee using fluoroscopy and then take the Rosenberg view. In the current series, we obtained standard radiographic series, but they were not corrected for magnification with marker films nor positioned using fluoroscopy; therefore, we did not include radiographic analysis in this study …. Although the early results of the combined procedure in otherwise salvage situations are inferior to either procedure in isolation, the potential of good and excellent results in this challenging population suggests the rationale for pursuing further multicenter studies.

In a case-series study, Gomoll et al (2014) hypothesized that repair of patellar cartilage defects with ACI will provide lasting improvements in pain and function. Patients were treated at 1 of 4 participating cartilage repair centers with ACI for cartilage defects in the patella; bipolar (patella + trochlea) defects were included as well. All patients were followed

prospectively for at least 4 years with multiple patient-reported outcome instruments, including the International Knee Documentation Committee, Short Form-12, modified Cincinnati Rating Scale, Western Ontario and McMaster Universities Osteoarthritis Index, and Knee Society scores. Treatment failure was defined as structural failure of the graft combined with pain requiring revision surgery. A total of 110 patients were available for analysis. As a group, they experienced both statistically significant and clinically important improvements in pain and function in all physical outcome scales. The International Knee Documentation Committee improved from 40 ± 14 pre-operatively to 69 ± 20 at the last follow-up; the Cincinnati Rating Scale, from 3.2 ± 1.2 to 6.2 ± 1.8; and the Western Ontario and McMaster Universities Osteoarthritis Index, from 50 ± 22 to 29 ± 22 (all $p < 0.0001$). Ninety-two percent of patients stated that they would choose to undergo ACI again, and 86 % rated their knees as good or excellent at the time of final follow-up. Nine patients (8 %) were considered treatment failures, and 16 % reported that their knees were not improved. The authors concluded that cartilage repair in the patella-femoral joint is arguably not without its challenges. Autologous chondrocyte implantation remains off-label in the patella, a fact that needs to be discussed with prospective patients during the informed consent process. However, when performed with attention to patella-femoral biomechanics, self-rated subjective good and excellent outcomes can be achieved in more than 80 % of patients treated with ACI, even in a patient population with large and frequently bipolar defects such as the one presented in this study. However, final functional scores, although significantly improved, still reflected residual disability in this challenging group of patients. One major drawback of this study was its non-randomized design (Thus, these findings only provided Level 4 evidence). Also, pathologic disorders vary substantially among patients, with cartilage defects of different sizes, locations, and numbers, as well as co-morbidities such as patellar mal-tracking, mal-alignment, meniscal and ligamentous deficiencies, and variability in body mass index.This study provided mid-term followup.

The authors stated that this study shared the limitations inherent to all non-randomized investigations; ACI is a rare procedure, with only approximately 1,500 cases performed annually in the United States, in comparison with approximately 600,000 knee replacement procedures. Furthermore, pathologic disorders vary substantially among patients, with

cartilage defects of different sizes, locations, and numbers, as well as co-morbidities such as patellar mal-tracking, mal-alignment, meniscal and ligamentous deficiencies, and variability in body mass index (BMI). As such, identifying and enrolling sufficiently uniform patients for randomized trials is challenging, as evidenced by the recent termination of 2 large phase II FDA clinical trials for new cartilage repair implants, owing to difficulty with enrollment (Zimmer DeNovo ET [Clinicaltrials.gov NCT01400607]; DePuy Mitek CAIS [Clinicaltrials.gov NCT00881023]). Specifically for patella-femoral cartilage repair studies, additional complexity is created by the lack of a reasonable procedure to act as control for randomization: techniques such as microfracture and OAT are considered problematic in the patella, with some authors reporting only transient pain relief and high failure rates. Debridement alone could be considered a control; however, patients are understandably reluctant to agree to palliative therapeutic options that provide only transient improvement, especially when considering that delaying cartilage repair has been associated with compromised outcomes. In an attempt to address some of the limitations inherent to single-surgeon, case series studies, these investigators pooled data from 4 large cartilage repair centers to increase numbers and minimize the influence of surgeon-specific variations in indications, surgical techniques, and patient populations. Data were collected prospectively, with each center having defined follow-up protocols for cartilage repair patients at the start of its database, enrolling initial patients more than a decade ago. The authors noted that cartilage repair in the patella-femoral joint is arguably not without its challenges; ACI remains off-label in the patella, a fact that needs to be discussed with prospective patients during the informed consent process.

In a case-series study, Pascual-Garrido and colleagues (2009a) stated that reported results of autologous chondrocyte implantation (ACI) for chondral lesions in the patella-femoral (PF) joint have been encouraging when combined with re-alignment procedures. These researchers examined the clinical results of a patient cohort undergoing ACI of the PF joint and elucidated characteristics associated with successful implantation. The cohort included 62 patients who underwent ACI of the PF joint. The mean defect size was 4.2 cm(2) (+/-1.6). The average age was 31.8 years (range of 15.8 to 49.4), and the average follow-up was 4 years (range of 2 to 7). Outcomes were assessed via clinical assessment

and established outcome scales, including the Lysholm, International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Scale (KOOS; included the 5 categories of Pain, Symptoms, Activities of Daily Living, Sport, and Quality of Life), Tegner, Cincinnati, and Short Form-12. Mean improvement in the pre-operative to post-operative scores was significant for the Lysholm (37-63, $p < 0.001$), International Knee Documentation Committee (31-57, $p < 0.001$), KOOS Pain (48-71, $p < 0.001$), KOOS Symptoms (51-70, $p < 0.001$), KOOS Activities of Daily Living (60-80, $p < 0.001$), KOOS Sport (25-42, $p < 0.001$), KOOS Quality of Life (24-49, $p < 0.001$), Short Form-12 Physical (38-41, $p < 0.05$), Cincinnati (43-63, $p < 0.005$), and Tegner (4-6, $p < 0.05$), but not for the Short Form-12 Mental. There was no statistical difference between outcomes in patients with a history of a previous failed cartilage procedure compared with those patients without a prior cartilage procedure ($p > 0.05$). Patients undergoing antero-medialization tended toward better outcomes than those without re-alignment; 44 % of patients needed a subsequent procedure. There were 4 clinical failures (7.7 %), which were defined as progression to arthroplasty or conversion to osteochondral allograft transplantation. The authors concluded that ACI is a viable therapeutic option for chondral defects of the PF joint. Combined ACI with antero-medialization improved outcomes more than ACI alone. Patients with failed prior cartilage procedures could also expect sustained and clinically meaningful improvement. This was a small case-series study with mid-term follow-up; it provided only Level 4 evidence.

The authors stated that the main weakness in this study was that they were unable to have a control group to compare with the 3 groups of patients. In the study, they had to use each subgroup for comparison and statistical analysis to determine clinical comparisons. A control group would have allowed further analysis to determine true improvement of each subgroup. Because of the nature of the study, these researchers were unable to randomize the groups. To truly examine if tibial tuberosity anteromedialization (AMZ) is beneficial concomitantly with PF ACI, a blinded randomized study with ACI alone or ACI with AMZ is needed. Another weakness in this study was a small number of patients in each subgroup analyzed and that the ACI group had less time to final follow-up in comparison with the other subgroups (30 months vs 4 years). Because ACI normally undergoes a process of maturation that in the majority of

cases took longer than 18 months, several studies have indicated that patients undergoing ACI should have a minimum follow-up of at least 2 years, after which the clinical improvement plateaus. However, the ACI group did statistically worse than patients treated with both AMZ and ACI, despite the shorter follow-up. One would expect the converse, perhaps indicating that AMZ together with ACI might prolong the effects of ACI. Additionally, there might have been a larger difference in outcomes between patients with ACI alone versus ACI with AMZ if the follow-up had been longer in patients with ACI alone.

In a prospective, observational study, Gigante et al (2009) evaluated the 3-year clinical outcome of distal realignment and membrane-seeded autologous chondrocyte implantation (MACI) in selected patients with patella-femoral mal-alignment and large, isolated, patellar cartilage lesions. A total of 12 patients (14 knees; 6 females, 6 males; mean age of 31 years) with Fulkerson type II patella-femoral mal-alignment (lateralized and tilted patella) and Outerbridge grade III-IV isolated patellar cartilage lesions were treated. All had tibial tuberosity and trochlear sulcus of greater than 20 mm on a pre-operative computed tomography (CT) scan and a cartilage defect greater than 3 cm2. Patients with Outerbridge grade III-IV trochlear cartilage lesions, those with rheumatic, infective or neoplastic conditions, or ligament instability, diabetes or obesity and those aged greater than 40 years were excluded. Follow-up was at 36 months. Patients were enrolled after diagnostic arthroscopy. Cartilage was harvested and sent for culture. After a mean period of 30 days (range of 25 to 40) patients underwent transfer of the tibial tuberosity according to Fulkerson associated with a MACI procedure. Clinical assessment was performed with the Kujala, Lysholm, Tegner and Modified Cincinnati scores. The Patient Satisfaction Survey was administered at 36 months. Consistently improved knee function and activity levels were reflected by significantly increased Kujala, Lysholm, Tegner and Modified Cincinnati scores at 36 months. The authors concluded that the significant clinical improvement supported the value of associating distal re-alignment and ACI in treating large, isolated, patellar cartilage lesions associated with patella-femoral mal-alignment. Moreover, they stated that larger series with longer follow-up are needed to establish the effectiveness and long-term durability of this therapeutic strategy. This study had several drawbacks. First, the small sample size (n = 12) and the 36-month follow-up did not prove that the technique is

effective in the longer term. Secondly, non-blinded post-operative assessment may have led to over-estimation of favorable outcomes, and lastly the study lacked a control group, although not treating one or the other condition would of course have posed an ethical problem.

In a case-series study, Gobbi et al (2009) hypothesized that hyaluronan-based scaffold seeded with autologous chondrocytes is a viable treatment for the damaged articular surface of the patella-femoral joint. Among a group of 38 patients treated for full-thickness patella-femoral chondral lesions with 2nd-generation ACI, these researchers examined 34 who were available for final follow-up at 5 years. These 34 had chondral lesions with a mean size of 4.45 cm(2); 21 lesions were located on the patella, 9 on the trochlea, and 4 patients had multiple lesions: 3 had patellar and trochlear lesions, and 1 had patellar and lateral femoral condyle lesions; 26 lesions (76.47 %) were classified as International Cartilage Repair Society (ICRS) grade IV A or B, 5 lesions (14.70 %) were grade IIIC, and 3 (8.82 %) were lesions secondary to osteochondritis dissecans (OCD). Results were evaluated using the International Knee Documentation Committee (IKDC) 2000 subjective and objective scores, EuroQol (EQ) visual analog scale (VAS), and Tegner scores at 2 and 5 years; 8 patients had second-look arthroscopy and biopsies. All the scores used demonstrated a statistically significant improvement ($p < 0.0005$) at 2 and 5 years' follow-up. Objective pre-operative data improved from 8 of 34 (23.52 %) normal or nearly normal knees to 32 of 34 (94.12 %) at 2 years and 31 of 34 (91.17 %) at 5 years after transplantation. Mean subjective scores improved from 46.09 points pre-operatively to 77.06 points 2 years after implantation and 70.39 at 5 years. The Tegner score improved from 2.56 to 4.94 and 4.68, and the EQ VAS improved from 56.76 to 81.47 and 78.23 at 2 and 5 years' follow-up, respectively. A significant decline of IKDC subjective and Tegner scores was found in patients with multiple and patellar lesions from 2 to 5 years' follow-up. Second-look arthroscopies in 8 cases revealed the repaired surface to be nearly normal with biopsy samples characterized as hyaline-like in appearance. The authors concluded that hyaluronan-based scaffold seeded with autologous chondrocytes can be a viable treatment for patella-femoral chondral lesions. Moreover, they stated that long-term follow-up (10 years) studies are needed to confirm the durability of the tissue repair produced with this new technique and to

identify particular patients who would benefit from it. Level of Evidence: IV. This was a small study (n = 21 for patellar lesions) with mid-term results (5 years).

Macmull et al (2012) evaluated the effectiveness of ACI on patients with a proven symptomatic retro-patellar lesion who had at least 1 failed conventional marrow-stimulating therapy. These researchers performed chondrocyte implantation on 48 patients: 25 received ACI with a type I/III membrane (ACI-C) method (Geistlich Biomaterials, Wolhusen, Switzerland), and 23 received the Matrix-assisted Chondrocyte Implantation (MACI) technique (Genzyme, Kastrup, Denmark). Over a mean follow-up period of 40.3 months, there was a statistically significant improvement in subjective pain scoring using the visual analog scale (VAS) and objective functional scores using the Modified Cincinnati Rating System (MCS) in both groups. The authors concluded that chondromalacia patellae lesions responded well to chondrocyte implantation. Better results occurred with MACI than with ACI-C. Excellent and good results were achieved in 40 % of ACI-C patients and 57 % of MACI patients, but success of chondrocyte implantation was greater with medial/odd-facet lesions. The authors concluded that symptomatic chondromalacia patellae lesions improved with chondrocyte implantation, especially in patients who received MACI. The longer a patient has symptoms and the more previous procedures, the worse the prognosis appeared to be. Patients had on average a seven year history and were often at a point where symptoms were severe, with constant pain and significant reduction in function. The authors considered that earlier intervention could have provided even better results in this often difficult group of patients; however, a larger study is needed to clarify this point. This was a relatively small study (n = 25 for the ACI group) with only mid-term results (40.3 months).

Nawaz and colleagues (2014) evaluated the functional outcomes in 827 of 869 patients who had undergone ACI with Chondron or periosteum (ACI-C/ACI-P) or MACI and attempted to identify factors that influenced outcome. The age of the patient, the size and site of the osteochondral lesion, previous surgery, and the presence of early osteoarthritis were assessed for their influence on outcomes. Each factor was evaluated in a separate Cox proportional hazards model with use of hazard ratios (HRs), with 95 % confidence intervals (CIs), describing the likelihood of failure

for that particular factor. Outcomes were assessed with use of the modified Cincinnati score, VAS pain score, and Stanmore functional score. The mean duration of follow-up was 6.2 years (range of 2 to 12 years). The mean age was 34 years (range of 14 to 56 years), with 493 males and 334 females. The average size of the defect was 409 mm2 (range of 64 to 2,075 mm2). A total of 421 procedures (51 %) were performed on the medial femoral condyle; 109 (13 %), on the lateral femoral condyle; 200 (24 %), on the patella; and 50 (6 %), on the trochlea. Kaplan-Meier survival analysis revealed that the un-adjusted graft survival rate was 78.2 % at 5 years and 50.7 % and 10 years for the entire cohort. No difference was found between the survival rates of the ACI-C/ACI-P and MACI techniques (HR = 0.948, 95 % CI: 0.738 to 1.219, p = 0.678). There was a significant post-operative improvement in the function and pain scores of all 3 outcome measures ($p < 0.002$). Survivorship in the group with a previous cartilage regenerative procedure was inferior to that in patients with a previously untreated lesion, with failure 5 times more likely in the former group (HR = 4.718, standard error [SE] = 0.742, 95 % CI: 3.466 to 6.420, $p < 0.001$). Degenerative change in any compartment had a significant detrimental effect on survivorship, with survivorship worsening as the osteoarthritis grade increased (Grade 1: HR = 2.077, 95 % CI: 1.299 to 3.322, p = 0.002; Grade 2: HR = 3.450, 95 % CI: 2.646 to 4.498, $p < 0.001$; and Grade 3: HR = 3.820, 95 % CI: 2.185 to 6.677, $p < 0.001$). The authors concluded that the findings of this study demonstrated an overall graft survival of 78 % at 5 years and 51 % beyond 10 years following both ACI techniques. They stated that despite study limitations, these results demonstrated that ACI for the treatment of osteochondral defects of the knee can achieved good results. This study provided mid-term results. Level of Evidence: IV.

Gillogly et al (2014) noted that isolated chondral lesions of the patella are particularly challenging to treat, and long-term studies of treated isolated patellar lesions are limited. Previous short-term studies have reported favorable outcomes of ACI of the patella and/or trochlea, with a trend toward improvement when antero-medialization (AMZ) of the tibial tubercle was performed with the procedure. In a case-series study, these researchers hypothesized that ACI with concomitant AMZ for symptomatic isolated patellar lesions provides functional and symptomatic improvement in patients at a minimum 5-year follow-up.

Patients with failed primary treatment of isolated patellar full-thickness articular cartilage defects and PF mal-alignment who were treated with ACI and AMZ of the tibial tubercle at least 5 years prior were contacted for final post-operative outcome scores. Outcome scales including the International Knee Documentation Committee (IKDC), Lysholm, modified Cincinnati Knee Rating System, and 12-item Short Form Health Survey (SF-12) scores were assessed at baseline and final follow-up. Of 27 eligible patients, 23 (25 knees) were available for assessment at a mean follow-up of 7.6 years (range of 5.1 to 11.4). Significant improvements from baseline to final follow-up were observed in the IKDC score (from 42.5 to 75.7; $p < 0.0001$), modified Cincinnati Knee Rating System score (from 3.0 to 7.0; $p < 0.0001$), Lysholm score (from 40.2 to 79.3; $p < 0.0001$), and SF-12 score (physical component score: from 41.2 to 47.6; $p = 0.002$; mental component score: from 48.1 to 60.7; $p = 0.0001$). Most patients (83 %; 19/23) rated their surgery as good or excellent. The overall re-operation rate was 40 % (10/25) largely because of periosteal hypertrophy (33 %); 1 patient failed at 5.9 years post-operatively and underwent PF arthroplasty. The authors concluded that combined ACI and AMZ resulted in significant improvements in symptoms and function with a low incidence of adverse events in patients with isolated symptomatic patellar chondral defects after a mean follow-up of more than 7 years. This was a small (n = 23) case-series study with mid-term (7.6 years) follow-up; it provided only Level 4 evidence.

The drawbacks of this study included the absence of a control or comparator group. It was the authors' opinion that a randomized study with a sham surgery would not be feasible or in the best interest of the patient because a sham surgery would not be beneficial to the patient. Furthermore, because they believed that the mechanical unloading and re-alignment that occurred with AMZ benefit chondral repair tissue, these researchers did not perform ACI without AMZ for patellar lesions and thus were unable to compare with a group that was treated with ACI alone. However, historical data showed that patellar lesions perform poorly when treated with ACI alone. In fact, a study by Henderson and Lavigne found that patients who had their patellar lesions treated with ACI and had their abnormal patellar tracking corrected did significantly better than patients who had their patellar lesions treated with ACI but who did not require re-alignment. Conversely, these investigators were also unable to compare their group of patients with patients who only underwent AMZ, as this

procedure is historically used to correct only patellar mal-alignment and not to treat chondral defects. Another drawback was the fact that TT-TG measurements were not performed on patients before 2006 when Schoettle et al reported a correlation between CT and magnetic resonance imaging (MRI) measurements. The TT-TG measurements provided an objective value for assessing patellar mal-tracking and also aided in determining the amount of anteriorization and medialization. Additionally, the small number of patients (n = 23 available for follow-up) limited the authors' ability to perform analyses between subgroups within various strata and tested for the effect of previous microfracture, defect classification, trochleoplasty, or workers' compensation status. However, subanalyses from pre-operative to post-operative score changes did indicate significant improvements in the modified Cincinnati Knee Rating System score, Lysholm score, as well as IKDC score for patients independent of lesion containment and defect classification (type IVb or others). Furthermore, because of the retrospective nature of this study, the authors were unable to contact some additional patients (n = 4) despite exhaustive search measures and therefore were unable to account for their status and include them in these analyses.

Niemeyer et al (2016) stated that treatment of cartilage defects of the knee remains an important issue with high relevance. In October 2013 the German Cartilage Registry (KnorpelRegister DGOU) was initiated in order to study indications, epidemiology and (clinical) outcome of different cartilage repair techniques. The present evaluation of the registry baseline data was initiated to report common practices of cartilage repair surgery in Germany. A total of 1,065 consecutive patients who underwent surgical cartilage treatment of the knee have been included (complete data sets available in 1,027 cases; FU rate 96.4 %) between October 1, 2013 and June 30, 2015. Data collection was performed using a web-based RDE System. All data were provided by the attending physician at the time of arthroscopic or open surgery of the affected knee. In 1,027 cartilage repair procedures, single defects were treated in 80 % of the cases with the majority of the defects located on the medial femoral condyle, followed by the patella. Degenerative defects grade III or IV according to ICRS were treated in 60 % of the cases and therefore were found more frequently compared to traumatic or post-traumatic lesions. Autologous chondrocyte implantation (ACI) was the most common technique followed by bone marrow stimulation (BMS) and osteochondral

transplantation (OCT). While ACI was performed in defects with a mean size of 4.11 cm(2) SD 2.16), BMS and OCT (1.51 cm(2), SD 1.19; $p < 0.01$) were applied in significantly smaller defects (both $p < 0.01$). Independent of defect size, the ratio of ACI versus BMS applications differed between different defect locations; ACI was used preferably in defects located on the patella. The authors concluded that present analysis of data from the German Cartilage Registry showed that the vast majority of cartilage repair procedures were applied in degenerative, non-traumatic cartilage defects. Experts in Germany appeared to follow the national and international guidelines in terms that bone marrow stimulation is applied in smaller cartilage defects while cell-based therapies are used for the treatment of larger cartilage defects. In patellar cartilage defects a trend towards the use of cell-based therapies has been observed.

There is emerging evidence for MACI in patellar lesions. Ebert and colleagues (2015) noted that while matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging outcomes in the treatment of patients with knee chondral defects, there remains little available research specifically investigating its use in the patella-femoral joint. In a case-series study, these researchers prospectively evaluated the clinical and radiologic outcome of MACI in the patella-femoral joint. In 47 consecutive patients undergoing patella-femoral MACI, clinical (Knee injury and Osteoarthritis Outcome Score, 36-Item Short Form Health Survey, visual analog scale for pain, 6-minute walk test, knee range of motion, and strength assessment) and magnetic resonance imaging (MRI) assessments were undertaken before and 3, 12, and 24 months after surgery. The MRI was performed to assess graft infill and determine an overall MRI composite score. Results were analyzed according to (i) the patient sample overall, and (ii) after stratification into 4 subgroups per implant location (patella or trochlea) as well as whether or not adjunct tibial tubercle transfer for patella-femoral mal-alignment was required. The overall patient sample, as well as each of the 4 procedural subgroups, demonstrated clinically and statistically significant ($p < 0.05$) improvements over time for all clinical scores. Graft infill and the MRI composite score also demonstrated statistically significant ($p < 0.05$) improvements over time, with no evidence of a main effect for procedure group or interaction

between procedure group and time. At 24 months after surgery, 40.4 % (n = 19) of patients exhibited complete graft infill comparable with the adjacent native cartilage, with a further 6.4 % (n = 3) demonstrating a hypertrophic graft. A further 31.9 % (n = 15) of patients exhibited 50 % to 100 % tissue infill, and 17 % (n = 8) demonstrated less than 50 % tissue infill; 2 patients (4.3 %) reported graft failure. At 24 months after surgery, 85 % (n = 40) of patients were satisfied with the results of their MACI surgery. The authors concluded that these results demonstrated that MACI provided improved clinical and radiologic outcomes to 24 months in patients undergoing treatment specifically for articular cartilage defects on the patella or trochlea, with and without concurrent realignment of the extensor mechanism if required (Level of evidence, 4). The main drawbacks of this study were its case-series design with a relatively small sample size (n = 47), and short-term follow-up (24 months).

Kon and associates (2016) stated that cartilage lesions of the patella-femoral joint are a challenging condition. Hyaluronan-based matrix-assisted autologous chondrocyte transplantation (MACT) has been shown to offer a significant improvement in the short-term but has a tendency to worsen at midterm follow-up. In a case-series study, these investigators examined if patients treated with MACT for lesions of the articular surface of the patella-femoral joint would present further clinical worsening at long-term follow-up. A total of 32 patients with full-thickness chondral lesions in the patella-femoral joint were treated with hyaluronan-based MACT and were prospectively evaluated pre-operatively and at 2-, 5-, and 10-year follow-up. The mean defect size was 4.45 cm(2). There were 20 lesions located on the patella and 8 on the trochlea, and 4 patients had multiple lesions: 3 with patellar and trochlear lesions and 1 with patellar and lateral femoral condyle lesions. Results were evaluated using International Knee Documentation Committee (IKDC) subjective scores, EuroQol visual analog scale (EQ VAS) scores, and Tegner scores. Surgical and clinical failures were documented. All scores showed a statistically significant improvement at 2-, 5-, and 10-year follow-up with respect to the pre-operative level. No worsening was observed at the last follow-up, and results were stable up to 10 years. The improvement in mean (± SD) outcome scores from pre-operatively to 2-, 5-, and 10-year follow-up was as follows: IKDC, from 46.0 ± 19.8 to 77.1 ± 17.4, 72.0 ± 20.4, and 78.6 ± 16.4, respectively; Tegner, from 2.5 ± 1.4 to 4.7 ± 1.8, 4.7 ± 1.6, and 4.4 ± 1.5, respectively; and EQ VAS, from

56.9 ± 18.4 to 81.7 ± 13.2, 79.2 ± 17.9, and 78.9 ± 1.7, respectively. Four patients did not achieve significant clinical improvement, and 1 of these patients required further surgical treatment. All failures were female patients with patellar defects, and 3 of them had degenerative lesions and underwent a previous or combined re-alignment procedure. The authors concluded that the clinical results of hyaluronan-based MACT treatment of chondral lesions of the patella-femoral joint did not worsen over time but remained stable and showed a low rate of failure at long-term follow-up (Level of evidence, 4). The main drawbacks of this study were its case-series design with a small sample size (n = 20).

Henderson and colleagues (2006) reported the clinical outcome of ACI patients with graft hypertrophy compared with that of un-operated ACI patients and longitudinally evaluated the effects of graft hypertrophy debridement. These researchers divided 170 knee ACI patients with a minimum of 2-year follow-up into groups according to the need for re-operation after ACI and the findings at surgery. Group A (n = 73) comprised patients who did not undergo re-operation, group B (n = 61) comprised patients who underwent re-operation and had findings unrelated to the repair, and group C (n = 36) comprised patients who underwent re-operation and had isolated graft hypertrophy. The International Knee Documentation Committee, modified Cincinnati knee rating, and SF-36 physical component scores for the 3 groups were compared. Of the repairs debrided because of graft hypertrophy, 41 were longitudinally assessed with arthroscopy or MRI. The mean follow-up was 42.2 months. Patch-related problems were seen in 73.7 % of cases undergoing re-operation less than 2 years after implantation, whereas cartilage-related problems were the dominant finding more than 2 years after implantation (70.2 %). Group A patients fared significantly better than group B or C patients with regard to all 3 parameters measured, with no difference between groups B and C. Longitudinal assessment of 41 hypertrophied repairs revealed 18 with signs of pathology after graft debridement. The authors concluded that the findings of this study showed that re-operation is frequent after ACI and is associated with a less satisfying outcome. Furthermore, debridement of a hypertrophied ACI graft appeared to be detrimental as shown by longitudinal assessment of repairs.

The authors stated that the main drawback of this study was that it reported the outcome and macroscopic characteristics of a symptomatic population of hypertrophied ACI repairs. Because graft hypertrophy may be asymptomatic and its natural history (whether it will become symptomatic) is unknown, the effect of debridement reported may not reflect the reality of all hypertrophied repairs. In addition, only a small number of patients with graft hypertrophy who had different repair characteristics (single and multiple repairs in different anatomic locations) and short-term to mid-term follow-up were studied. All of these variables, though not different between the 3 groups, as well as the fact that some patients had concomitant knee pathology not related to the repair, may have affected data analysis. Finally, combining observations from arthroscopy and MRI may also affected the validity of the conclusions despite the fact that a good correlation exists between these 2 modalities in ACI repair assessment.

Farr (2008) stated that patella-femoral articular cartilage lesions are challenging to treat. While treatment with tibial tuberosity AMZ is effective for isolated distal lateral patellar lesions, other patellar or trochlear lesions have suboptimal outcomes with AMZ. Historically, when ACI was used at the patella-femoral compartment without optimizing the contact areas, the results were poor. In recent years, the combination of AMZ and ACI has yielded overall outcomes superior to either technique used in isolation for large patellar and trochlear chondral lesions. The author noted that the role of AMZ appeared to be important in those patients with mal-alignment, but the clinical experience of the surgeons is difficult to objectively communicate based on the available data. It may be useful, in the future, to evaluate patients pre- and post-operatively for PF contact areas similar to the finite element analysis (FEA) modeling of Ateshian and Cohen, as well as measurement of the tibial tuberosity-trochlear groove distance (TT-TG) and then correlate these with outcomes in an effort to further add objectively. Hopefully, by using objective data points pre-operatively, the optimal use of AMZ with ACI may be elucidated. These case series support the safety and efficacy of PF ACI in the short and intermediate term

Peterson and associates (2010) stated that the mid-term results of ACI have shown good-to-excellent outcomes for the majority of patients. However, no long-term results 10 to 20 years after the surgery have been

reported. In a case-series study, these researchers examined if ACI provides a durable solution to the treatment of full-thickness cartilage lesions of the knee, maintaining good clinical results even 10 to 20 years after implantation. In an uncontrolled, case-series study, questionnaires with the Lysholm, Tegner-Wallgren, Brittberg-Peterson, modified Cincinnati (Noyes), and Knee Injury and Osteoarthritis Outcome Score (KOOS) scores were sent to 341 patients. Pre-operative Lysholm, Tegner-Wallgren, and Brittberg-Peterson scores were also retrieved when possible from patients' files. Patients were asked to grade their status during the past 10 years as better, worse, or unchanged. Finally, they were asked if they would do the operation again. There were 224 of 341 patients (65.7 %) who replied to the posted questionnaires and were assessed. The mean cartilage lesion size was 5.3 cm(2); 10 to 20 years after the implantation (mean of 12.8 years), 74 % of the patients reported their status as better or the same as the previous years. There were 92 % who were satisfied and would have the ACI again. The Lysholm, Tegner-Wallgren, and Brittberg-Peterson scores were improved compared with the pre-operative values. The average Lysholm score improved from 60.3 pre-operatively to 69.5 post-operatively, the Tegner from 7.2 to 8.2, and the Brittberg-Peterson from 59.4 to 40.9. At the final measurement, the KOOS score was on average 74.8 for pain, 63 for symptoms, 81 for activities of daily living (ADL), 41.5 for sports, and 49.3 for QOL. The average Noyes score was 5.4. Patients with bipolar lesions had a worse final outcome than patients with multiple unipolar lesions. The presence of meniscal injuries before ACI or history of bone marrow procedures before the implantation did not appear to affect the final outcomes. The age at the time of the operation or the size of lesion did not appear to correlate with the final outcome. The authors concluded that ACI has emerged as an effective and durable solution for the treatment of large full-thickness cartilage and osteochondral lesions of the knee joint. They stated that the findings of this study suggested that the clinical and functional outcomes remained high even 10 to 20 years after the implantation. Level of evidence: IV.

The authors stated that this study had several drawbacks, most of them associated with the longitudinal nature of the study (lack of a control group) and the retrospective way of collecting pre-operative data. They stated that the response rate was 65.7 %; although this number was lower than the recommended limit of 70 %; and implied a reduced

reliability of our results, it might appear as an acceptable rate given the long-term of follow-up as many treated patients could not be reached or tracked. Moreover, many of the included patients were not followed during the last years; that made it impossible to report the complication rate and any procedures performed during those years in a reliable way. Not all of the questionnaires had been answered pre-operatively, as previously mentioned, reducing the power of the statistical comparisons. Furthermore, as there was no control group, no comparison can be made with the non-operative treatment of cartilage lesions or with other possible surgical treatments. In addition, despite the improvement shown in all questionnaires, it remained questionable whether the amount of improvement was clinically significant.

Gille et al (2016) conducted a prospective case series to evaluate long-term outcomes in patients who were treated with MACI. Inclusion criteria were patients between 18 and 60 years old with localized cartilage defects. Exclusion criteria were inflammatory arthritis, total meniscectomy, knee instability, an inoperable valgus or varus deformity, patellofemoral dysplasia, and massive overweight (body mass index >35 kg/m2). Thirty-eight patients were evaluated for up to a mean of 16 years after the MACI intervention. Three different scores (Lysholm-Gilquist score, International Cartilage Repair Society score, and Tegner score) formed the basis of this study. Follow-up of 15 knees was performed in this series. In subjective rating, 12 out of 14 patients (86%) rated the function of their knee as much better or better than before the index procedure. All numerical outcome scores showed significant improvement compared to the preoperative value (preoperative/postoperative at 5 years/postoperative at 15 years): Lysholm score 59.6, International Knee Documentation Committee score 50.6, Tegner score 3.0. The authors concluded that their results showed significant improvement on 3 scores after 15 years which suggest that MACI is a suitable treatment of local cartilage defects in the knee.

Ebert et al (2017) conducted a cohort study to compare the radiological and clinical outcomes of those undergoing MACI to either the femoral condyles or patellofemoral (PF) joint. The authors noted that earlier studies suggested that chondrocyte implantation in the PF joint was less effective than in the tibiofemoral (TF) joint. “A total of 194 patients were included in this analysis, including 127 undergoing MACI to the medial (n

= 94) and lateral (n = 33) femoral condyle, as well as 67 to the patella (n = 35) or trochlea (n = 32). All patients were evaluated clinically (Knee injury and Osteoarthritis Outcome Score [KOOS], visual analog scale, Short Form–36) before surgery and at 3, 12, and 24 months after surgery, while MRI was undertaken at 3, 12, and 24 months, with the MOCART (magnetic resonance observation of cartilage repair tissue) scoring system employed to evaluate the quality and quantity of repair tissue, as well as an MRI composite score. Patient satisfaction was evaluated. No significant group differences (P =.05) were seen in demographics, defect size, prior injury, or surgical history, while the majority of clinical scores were similar preoperatively. All clinical scores significantly improved over time (P\.05), with a significant group effect observed for KOOS activities of daily living (P = .008), quality of life (P = .008), and sport (P = .017), reflecting better postoperative scores in the TF group. While the PF group had significantly lower values at baseline for the KOOS activities of daily living and quality of life subscales, it actually displayed a similar net improvement over time compared with the TF group. At 24 months, 93.7% (n = 119) and 91.0% (n = 61) of patients were satisfied with the ability of MACI to relieve their knee pain, 74.0% (n = 94) and 65.7% (n = 44) with their ability to participate in sport, and 90.5% (n = 115) and 83.6% (n = 56) satisfied overall, in the TF and PF groups, respectively. MRI evaluation via the MOCART score revealed a significant time effect (P\.05) for the MRI composite score and graft infill over the 24-month period. While subchondral lamina scored significantly better (P = .002) in the TF group, subchondral bone scored significantly worse (P\.001). At 24 months, the overall MRI composite score was classified as good/excellent in 98 TF patients (77%) and 54 PF patients (81%).” The authors concluded that “MACI in the PF joint with concurrent correction of PF maltracking if required leads to similar clinical and radiological outcomes compared with MACI on the femoral condyles.” LOE, 3.

Noted limitations noted per Ebert and colleague (2017) included the primary method of clinical assessment. The investigators used the KOOS score, which, they note, has been shown to be very responsive to improvement after MACI surgery. However, there are a number of other PRO measures that have been used to assess ACI50 which may be able to better differentiate differences in patients undergoing TF and PF joint surgery. Furthermore, despite the differences observed in sport satisfaction, [they] did not employ any functional (ie, single-limb hop tests,

isokinetic knee strength assessment) or activity-based outcome measures (ie, Tegner, Noyes, or Marx Activity Scales), which would have given us additional information on group performance. Second, in the 26 patients for whom PF MACI was combined with a proximal (lateral release) or distal (TTT) realignment procedure, the clinical result was the sum of these combined interventions. Therefore, the specific effect of each individual procedure could not be assessed. However, [they] believe that the encouraging results for PF MACI in this study are largely attributed to the fact that PF maltracking was corrected at the same time and that assessment of each component is irrelevant. Furthermore, it is likely that a realignment procedure on its own would have not provided the regenerated tissue observed on MRI, as a result of the MACI procedure. Finally, the MOCART score that was used compares repair tissue to the native adjacent cartilage. It shows that ACI often results in a repair tissue with similar MRI appearance to the surrounding native cartilage.

Von Keudell et al (2017) conducted a prospective study to evaluate patients with patella defects treated with ACI at medium- to long-term follow-up. Thirty consecutive patients with isolated chondral lesions of the patella were enrolled prospectively. Primary outcome measures were validated from patient reported outcome measures and objective MRI. Nineteen of 30 patients underwent tibial tubercle osteotomy (TTO) to correct lateral maltracking in combination with soft tissue balancing. The defect sizes were large (range 2.2-30.0 cm2). Pidoriano/Fulkerson classification revealed that 3 defects were type II (lateral), 9 were type III (medial), and 18 were type IV (central/panpatella). Age at the time of surgery was 32 ± 10 years. At follow-up of 2 to 14 years, knee function was rated good to excellent in 83% patients, fair 13% patients, and poor 3%. Three patients failed treatment after a mean of 75 months. Significant increases in all clinical and health utility outcome scores were seen. MRI demonstrated that the fill grade, surface and integrity of the repair tissue correlated with clinical scores. The authors concluded that “ACI to isolated patella defects results in significant functional improvement at a minimum of 24 months, with the results remaining durable at latest follow-up of 15 years". LOE: 4.>

Krill et al (2018) conducted a literature review to evaluate the treatment of autologous chondrocyte implantation (ACI) for knee cartilage defects. The authors note that the most common locations for chondral lesions in the knee in athletes are the patellofemoral joint (37%), including the trochlea (24%) and patella (13%), followed by the femoral condyle (25%) and the tibial plateau (25%). “The goal of cartilage-restoration procedures is to reconstitute the native articular surface with mature and organized hyaline or hyaline-like cartilage”. The application of chondrocytes within a matrix was created to improve cell delivery and allow for minimally invasive implantation in order to better replicate normal cartilage architecture, thus accelerating patient rehabilitation. The authors believe that ACI is an effective technique for the treatment of articular cartilage lesions in appropriately selected patients, and that ACI results are improved if the cartilage lesions are treated within 12 to 18 months after the initial onset of symptoms.

Meniscal Allograft Transplantation with ACI

Rue et al (2008) noted that simultaneous combined meniscal allograft transplantation and cartilage restoration procedures have been proposed for patients with a symptomatic post-meniscectomy knee with a focal chondral defect that would have traditionally been considered a contraindication to meniscal allograft transplantation. These researchers hypothesized that combined meniscal allograft transplantation and cartilage restoration procedures can be used to neutralize traditional contraindications to meniscal allograft transplantation with results comparable to either procedure performed in isolation. A total of 30 patients underwent 31 combined meniscal allograft transplantation and cartilage restoration procedures between 1997 and 2004. These patients were prospectively studied, and completed standardized outcome surveys (including Lysholm, International Knee Documentation Committee, and Short Form-12 scales) preoperatively and annually thereafter for a minimum of 2-year follow-up. Patients were grouped according to concomitant procedure: 16 (52 %) underwent meniscal allograft transplantation combined with autologous chondrocyte implantation; 15 (48 %) had meniscal allograft transplantation combined with an osteochondral allograft. Two patients were lost to follow-up, leaving 29 procedures for review. As a combined group, statistically significant improvements were observed in all standardized outcomes

scores and satisfaction scales, except Short Form-12 mental, at a mean 3.1-year follow-up. Excluding the 2 lost to follow-up, 76 % of all study participants (80 % autologous chondrocyte implantation; 71 % osteochondral allograft) reported that they were completely (31 %) or mostly (45 %) satisfied with their results. Overall, 48 % of patients (60 % autologous chondrocyte implantation; 36 % osteochondral allograft) were classified as normal or nearly normal at their most recent follow-up using the International Knee Documentation Committee examination score. Ninety percent of patients would have the surgery again. The authors concluded that combined meniscal allograft transplantation and cartilage restoration offers a safe alternative for patients with persistent symptoms after meniscectomy and focal cartilage injury. They noted that results of combined procedures were comparable to published reports of these procedures performed in isolation; and long-term follow-up is needed to define the survivorship of these procedures in a young patient population.

In a systematic review of combined meniscal allograft transplantation and cartilage repair or restoration, Harris et al (2011) concluded that “Clinical outcomes after combined MAT and cartilage repair/restoration are similar to those after either procedure in isolation. Despite low rates of complications and failures, there is a high rate of subsequent surgery after combined MAT and cartilage repair or restoration”.

In a case-series study, McNickle and colleagues (2009) examined the clinical results of a patient cohort undergoing ACI and elucidated factors associated with subjective improvement after implantation. The cohort included 137 subjects (140 knees) who underwent ACI of the knee. Mean defect size per patient was 5.2 +/- 3.5 cm(2) (range of 0.8 to 26.6 cm(2)). Patients averaged 30.3 +/- 9.1 years of age (range of 13.9 to 49.9 years) and were followed for 4.3 +/- 1.8 years (range of 2.0 to 9.7 years). Outcomes were assessed via clinical assessment and established outcome scales, including the Lysholm scale, International Knee Documentation Committee scale, and Short Form-12. A significant improvement after surgery was observed in all outcome assessments including the Lysholm (41 to 69; $p < 0.001$) and International Knee Documentation Committee (34 to 64; $p < 0.001$) scales. Subjectively, 75 % of patients indicated they were completely or mostly satisfied with the outcome and 83 % would have the procedure again. Pre-operatively, 32 % of patients had a Tegner score of 6 or greater, compared with 82 %

before injury and 65 % at most recent follow-up. Multi-variate analysis identified age ($p < 0.021$) and receiving workers' compensation ($p < 0.018$) as independent predictors of follow-up Lysholm score. Twenty-one patients (16 %) required debridement of the ACI site secondary to persistent symptoms, whereas 9 knees (6.4 %) clinically failed and underwent a revision procedure. The authors stated that ACI is a viable treatment option for chondral defects of the knee, resulting in durable functional and symptomatic improvement. Age and workers' compensation status are independent predictors of outcome.

Moreover, the authors noted that "[a]lthough this study was able to assess the outcomes of a large cohort of patients treated with ACI, its retrospective design has several limitations. No control or comparison group was followed, and these patients were not randomized into treatment groups. Additionally, there were no set protocols for consistent reimaging or second-look arthroscopy. For the majority of patients, these options were only pursed with ongoing symptoms. Although the overall cohort size was large, several of the subsets (e.g., lesion location and concurrent procedures) were sufficiently small so as to underpower the multivariate analysis of their effects".

ACI of Talus

Nam et al (2009) reported the first U.S. prospective study of ACI of the talus. A total of 11 patients (6 women and 5 men; mean age of 33 years) underwent ACI of the talus after previous failed surgical management. There were 9 medial and 2 lateral lesions, with a mean size of 21 x 13 mm (273 mm2). Five patients underwent ACI of the talus alone; 6 had it with a "sandwich procedure." Ten patients underwent a second-look arthroscopy with screw removal. Mean follow-up was 38 months. Pre-operatively, 10 patients rated their ankles as poor and 1 as fair, using the simplified symptomatology evaluation. At latest follow-up, 3 patients were classified as excellent, 6 as good, and 2 as fair. Tegner activity level improved from 1.3 +/- 1.0 (mean +/- SE) pre-operatively to 4.0 +/- 1.6 ($p < 0.002$) post-operatively. The Finsen score (modified Weber score) showed significant improvement in the total score ($p < 0.001$). There was also overall agreement between the Finsen score and the American Orthopaedic Foot and Ankle Society ankle hindfoot score, with significant improvement from 47.4 +/- 17.4 preoperatively to 84.3 +/- 8.1 post-

operatively ($p < 0.001$). At repeat arthroscopy, complete coverage of the defect was seen in all patients. The authors concluded that ACI of the talus yields significant functional improvement; however, further investigation is necessary to determine the long-term structural and biomechanical properties of the repair tissue.

In a meta-analysis, Niemeyer et al (2012) evaluated the effectiveness of ACI for talar lesions. An OVID-based literature search was performed to identify any published clinical studies on autologous chondrocyte implantation (ACI) for the treatment of pathologies of the ankle including the following databases: MEDLINE, MEDLINE preprints, EMBASE, CINAHL, Life Science Citations, British National Library of Health, and Cochrane Central Register of Controlled Trials (CENTRAL). Literature search period was from the beginning of 1994 to February 2011. Of 54 studies that were identified, a total of 16 studies met the inclusion criteria of the present meta-analysis. Those studies were systematically evaluated. All studies identified represented case series (EBM Leven IV). A total of 213 cases with various treatment for osteochondral and chondral defects with a mean size of 2.3 cm(2) (+/- 0.6) have been reported. A total of 9 different scores have been used as outcome parameters. Mean study size was 13 patients (SD 10; range of 2 to 46) with a mean follow-up of 32 +/- 27 months (range of 6 to 120). Mean Coleman Methodology Score was 65 (SD 11) points. Overall clinical success rate was 89.9 %. The authors concluded that evidence concerning the use of ACI for osteochondral and chondral defects of the talus is still elusive.

DeSandis and colleagues (2018) stated that juvenile allogenic chondrocyte implantation (JACI; DeNovo NT Natural Tissue Graft®; Zimmer, Warsaw, IN) with autologous bone marrow aspirate concentrate (BMAC) is a relatively new all-arthroscopic procedure for treating critical-size osteochondral lesions (OCLs) of the talus. Few studies have investigated the clinical and radiographic outcomes of this procedure. These researchers collected the clinical and radiographic outcomes of patients who had undergone JACI-BMAC for talar OCLs to assess treatment efficacy and cartilage repair tissue quality using MRI. A total of 46 patients with critical-size OCLs (greater than or equal to 6 mm widest diameter) received JACI-BMAC from 2012 to 2014. These investigators performed a retrospective medical record review and assessed the

functional outcomes pre- and post-operatively using the Foot and Ankle Outcome Score (FAOS) and SF-12-item general health questionnaire; MRI was performed pre-operatively and at 12 and 24 months post-operatively. Cartilage morphology was evaluated on post-operative MRI scans using the magnetic resonance observation of cartilage tissue (MOCART) score. The pre- to post-operative changes and relationships between outcomes and lesion size, bone grafting, lesion location, instability, hypertrophy, and MOCART scores were analyzed. Overall, the mean questionnaire scores improved significantly, with almost every FAOS subscale showing significant improvement post-operatively. Concurrent instability resulted in more changes that were statistically significant. The use of bone grafting and the presence of hypertrophy did not result in statistically significant changes in the outcomes. Factors associated with outcomes were lesion size and hypertrophy. Increasing lesion size was associated with decreased FAOS quality of life (QOL) subscale and hypertrophy correlating with changes in the pain subscale. Of the 46 patients, 22 had undergone post-operative MRI scans that were scored. The average MOCART score was 46.8. Most patients demonstrated a persistent bone marrow edema pattern and hypertrophy of the reparative cartilage. The authors concluded that juvenile articular cartilage implantation of the DeNovo NT allograft and BMAC resulted in improved functional outcome scores; however, the reparative tissue still exhibited fibrocartilage composition radiographically. Moreover, they stated that further studies are needed to examine the long-term outcomes and determine the superiority of the arthroscopic DeNovo procedure compared with micro-fracture (MF) and other cartilage resurfacing procedures.

Karnovsky and associates (2018) compared the functional and radiographic outcomes of patients who received JACI-BMAC for treatment of talar OCLs with those of patients who underwent MF. A total of 30 patients who underwent MF and 20 who received DeNovo NT for JACI-BMAC treatment between 2006 and 2014 were included. Additionally, 17 MF patients received supplemental BMAC treatment. Retrospective chart review was performed and functional outcomes were assessed pre- and post-operatively using the FAOS and VAS. Post-operative magnetic resonance images were reviewed and evaluated using a modified MOCART score. Average follow-up for functional outcomes was 30.9 months (range of 12 to 79 months).

Radiographically, average follow-up was 28.1 months (range of 12 to 97 months). Both the MF and JACI-BMAC showed significant pre- to post-operative improvements in all FAOS subscales; VAS also showed improvement in both groups, but only reached a level of statistical significance ($p < 0.05$) in the MF group. There were no significant differences in patient reported outcomes between groups. Average OCL diameter was significantly larger in JACI-BMAC patients compared to MF patients, but size difference had no significant impact on outcomes. Both groups produced reparative tissue that exhibited a fibrocartilage composition. The JACI-BMAC group had more patients with hypertrophy exhibited on MRI than the MF group ($p = 0.009$). The authors concluded that JACI-BMAC and MF resulted in improved functional outcomes. However, while the majority of patients improved, functional outcomes and quality of repair tissue were still not normal. Based on these findings, lesions repaired with DeNovo NT allograft still appeared fibrocartilaginous on MRI and did not result in significant functional gains as compared to MF.

Matrix-Induced Autologous Chondrocyte Implantation (MACI)

The Bio-Gide, a resorbable bilayer membrane, consists of highly purified collagen types I and III (porcine origin). The membrane is highly biocompatible and supports wound healing. The three-dimensional (3D), natural fiber structure promotes cell adhesion, serves as a matrix for soft tissue support and provides a barrier to the ingrowth of overlying soft tissue into underlying bony defects. According to the product labeling, the Bio-Gide is used in dental surgery. There is a lack of evidence in the peer-reviewed literature on the use of Bio-Gide for ACT procedures.

The traditional ACT technique entails injection of a suspension of cells into the cartilage defect, which is covered with a periosteal flap or collagen membrane. This procedue requires extensive suturing to create an effective seal; however, cell leakage remains a potential problem. Matrix-induced autologous chondrocyte implantation (MACI) circumvents this potential problem by using a membrane on which chondrocytes are seeded and cultured for several days, before the membrane is cut to the correct size and shape of the defect. As a consequence, time-consuming extensive suturing is unnecessary.

Bartlett et al (2005) performed a prospective, randomized comparison of ACI-C and MACI for the treatment of symptomatic chondral defects of the knee in 91 patients, of whom 44 received ACI-C and 47 MACI grafts. Both treatments resulted in improvement of the clinical score after 1 year. The mean modified Cincinnati knee score increased by 17.6 in the ACI-C group and 19.6 in the MACI group (p = 0.32). Arthroscopic assessments performed after 1 year showed a good to excellent International Cartilage Repair Society score in 79.2 % of ACI-C and 66.6 % of MACI grafts. Hyaline-like cartilage or hyaline-like cartilage with fibrocartilage was found in the biopsies of 43.9 % of the ACI-C and 36.4 % of the MACI grafts after 1 year. The rate of hypertrophy of the graft was 9 % (4 of 44) in the ACI-C group and 6 % (3 of 47) in the MACI group. The frequency of re-operation was 9 % in each group. The authors concluded that the clinical, arthroscopic and histological outcomes are comparable for both ACI-C and MACI. While MACI is technically attractive, further long-term studies are required before the technique is widely adopted.

Zheng et al (2007) noted that MACI has been a treatment of cartilage injury since 2000, but little is known of the histological paradigm of tissue regeneration after implantation. MACI is a stable cell-based delivery system that enables the regeneration of hyaline-like cartilage. From a cohort of 56 MACI patients, these researchers examined the phenotype of chondrocytes seeded on type I/III collagen scaffold, and conducted progressive histological assessment over a period of 6 months. Chondrocyte-seeded collagen scaffolds from patient implants were analyzed by electron microscopy, immunohistochemistry (type II collagen and S-100), and reverse transcription polymerase chain reaction (RT-PCR) (aggrecan and type II collagen). Co-incidental cartilage biopsies were obtained at 48 hours, 21 days, 6 months, 8 months, 12 months, 18 months, and 24 months. These findings showed that chondrocytes on the collagen scaffold appeared spherical, well-integrated into the matrix, and maintained the chondrocyte phenotype as evidenced by aggrecan, type II collagen, and S-100 expression. Progressive histological evaluation of the biopsies showed the formation of cartilage-like tissue as early as 21 days, and 75 % hyaline-like cartilage regeneration after 6 months. The authors stated that this preliminary study has suggested that MACI may offer an improved alternative to traditional treatments for cartilage injury by regenerating hyaline-like cartilage as early as 6 months after surgery.

Ebert et al (2008) determined the effectiveness of "accelerated" compared to "traditional" post-operative load bearing rehabilitation protocols following MACI. A randomized controlled study design was used to investigate clinical, biomechanical and radiographic assessment at 3 months post-surgery in 62 patients following MACI to the medial or lateral femoral condyle. Both rehabilitation interventions sought to protect the implant for an initial period, then incrementally increase load bearing. Under the "accelerated" protocol, patients reached full weight bearing at 8 weeks post-surgery, compared to 11 weeks for the "traditional" group. Patients in the "accelerated" group achieved greater 6 min-walk distances and daily activity levels as measured by accelerometry ($p < 0.05$) compared to the "traditional" group. Furthermore, the "accelerated" group reported significantly better improvement in knee pain at 12 weeks as indicated by the Knee Injury and Osteoarthritis Outcome Score ($p < 0.05$), and regardless of the rehabilitation protocol employed, no patient suffered any adverse effect to the implant as assessed by magnetic resonance imaging at 3 months. Comparison of each rehabilitation group with an unaffected control group revealed a significant difference in peak knee adduction and flexion moments for the traditional group ($p < 0.05$). However, there was no difference for accelerated patients ($p > 0.05$), which may demonstrate a faster return to knee loading patterns typically observed in unaffected subjects. The authors concluded that the "accelerated" load bearing approach that reduced the length of time spent ambulating on crutches resulted in reduced knee pain, improved function, no graft complications and may speed up the recovery of normal gait function. They stated that patient follow-up to at least 24 months would be required to observe longer-term graft outcomes.

Safran et al (2008) stated that managing articular cartilage injury continues to be a difficult challenge for the clinician. Although the short- and intermediate-term results of autologous chondrocyte implantation appear to be favorable, resources are being directed toward research to improve the technology. One promising area of investigation is the combination of cultured chondrocytes with scaffolds. Clinicians desire techniques that may be implanted easily, reduce surgical morbidity, do not require harvesting of other tissues, exhibit enhanced cell proliferation and maturation, have easier phenotype maintenance, and allow for efficient and complete integration with surrounding articular cartilage. The characteristics that make scaffolds optimal for clinical use are that they be

biocompatible, biodegradable, permeable, reproducible, mechanically stable, non-cytotoxic, and capable of serving as a temporary support for the cells while allowing for eventual replacement by matrix components synthesized by the implanted cells. Clinical experience is growing with 3 scaffold-based cartilage repair techniques, each using a different type of scaffold material: (i) MACI, (ii) a hyaluronic acid-based scaffold, and (iii) a composite polylactic/polyglycolic acid polymer fleece. The authors stated that clinical results are encouraging; future directions in scaffold-based cartilage repair include bioactive and spatially oriented scaffolds.

Brittberg (2010) reviewed the current evidence of the MACI procedure; and iscussed the characteristics of type I/III collagen membranes, behavior of cells associated with the membrane, surgical technique, rehabilitation, clinical outcomes, and quality of repair tissue. Relevant publications were identified by searching Medline from its inception (1949) to December 2007; peer-reviewed publications of preclinical and clinical cell behavior, manufacturing process, surgical technique, and rehabilitation protocols were identified. Pre-clinical and clinical studies were included if they contained primary data and used a type I/III collagen membrane. Data from these studies demonstrated that patients treated with MACI have an overall improvement in clinical outcomes. Reduced visual analog scale pain levels (range of 1.7 to 5.32 points) and improvements in the modified Cincinnati (range of 3.8 to 34.2 points), Lysholm-Gillquist (range of 23.09 to 47.6 points), Tegner-Lysholm (range of 1.39 to 3.9 points), and International Knee Documentation Classification scale ($p < 0.05$) were observed. Patients had good-quality (hyaline-like) repair tissue as assessed by arthroscopic evaluation (including International Cartilage Repair Society score), magnetic resonance imaging, and histology, as well as a low incidence of post-operative complications. The author concluded that the findings suggested that MACI is a promising third-generation cell therapy for the repair of symptomatic, full-thickness articular cartilage defects.

Giza et al (2010) evaluated the results of MACI for the treatment of osteochondral defects of the talar dome using a technique that does not require an osteotomy of the tibia or fibula. A prospective investigation of MACI was performed on 10 patients with full-thickness lesions of the talus. Participants had a documented talus lesion on MRI, failure of

conservative treatment and arthroscopic debridement/curettage, persistent ankle pain and swelling, the absence of tibiotalar arthritis and a stable ankle. A total of 5 males and 5 females, with an average of 1.7 previous procedures prior to MACI, were included in this study. All patients were available for follow-up at 1 and 2 years. Lesions were graded during the harvesting procedure using the Cheng-Ferkel grading system, the Outerbridge classification, and the International Cartilage Repair Society system. Clinical and functional evaluation was done pre-operatively, and at 1 and 2 years post-operatively using the American Orthopaedic Foot and Ankle Society (AOFAS) hind-foot evaluation and the SF-36 Health Survey. Pre-operative AOFAS hind-foot scores were 61.2 (range of 42 to 76) that improved 1 year post-operatively to 74.7 (range of 46 to 87) ($p < 0.05$) and 2 years post-operatively to 73.3 (range of 42 to 90) ($p = 0.151$). At both 1 and 2 years post-operatively, the results of the SF36 evaluation demonstrated a significant improvement in the Physical Functioning ($p = 0.002$) and Bodily Pain ($p < 0.001$) components. Subjectively, all 10 patients believed this procedure helped them. The authors concluded that these findings suggest that MACI may be an effective way to treat full-thickness lesions of the talus using harvested chondrocytes from the talus without malleolar osteotomy. The results of this small study need to be validated by well-designed studies.

Ebert et al (2010) examined knee biomechanics during gait in 61 patients following MACI, in conjunction with either "accelerated" or "traditional" approaches to post-operative weight-bearing rehabilitation. Gait analysis was performed at 3, 6 and 12 months post-surgery in both patient groups, and 2 matched, unaffected control groups for comparison. The spatio-temporal and ground reaction force parameters were similar between patient groups and their respective control groups at all time points. When compared with controls, both patient groups demonstrated significantly reduced knee extension moments up until, and including, 12 months. The traditional group demonstrated a significantly reduced knee adduction moment at 3, 6 and 12 months, and a significantly reduced knee flexion moment at 3 months. There were no differences in these knee moments between the accelerated patient group and controls. The authors concluded that overall, a higher level of gait dysfunction was observed in patients who underwent traditional rehabilitation. They stated that future research is needed to investigate the recovery of normal gait following MACI, and its effect on repair tissue development.

Genovese et al (2011) defined magnetic resonance (MR) arthrography imaging findings of MACI grafts of the knee in order to describe implant behavior and compared findings with validated clinical scores 30 and 60 months after MACI implant. A total of 13 patients were recruited (3 females and 10 males) with a total number of 15 chondral lesions. Each patient underwent an MACI procedure and MR arthrography 30 and 60 months after surgery. Magnetic resonance arthrography was performed using a dedicated coil with a 1.5-Tesla unit. The status of the chondral implant was evaluated with the modified MOCART scoring scale. The lining of the implant, the integration to the border zone, the surface and structure of the repaired tissue were assessed, and the presence of bone marrow edema and effusion was evaluated. For clinical assessment, the Cincinnati score was used. At 60 months, the abnormality showed worsening in 1 out of 15 cases. Integration showed improvement in 3 out of 15 cases, and worsening in 3 out of 15 cases. Two surfaces of the implant showed further deterioration at 60 months, and 1 afflicted implant fully recovered after the same time interval. Implant contrast enhancement at 30 months was seen in 2 out of 15 cases, 1 of which recovered at 60 months. According to the MOCART score, 4 cases were rated 68.4 out of 75 at 30 months and 65 out of 75 at 60 months. The mean clinical score decreased from 8.6 out of 10 at 30 months to 8.1 out of 10 at 60 months. The authors concluded that MR arthrography improved the evaluation of implants and facilitated the characterisation of MACI integration with contiguous tissues. The follow-up showed significant changes in MACI, even at 60 months, allowing for useful long-term MR evaluations.

Benthien et al (2011) performed a systematic review of studies concerning current treatment of chondral defects of the knee. The relevance for evidence based data and for successful surgical treatment of cartilage defects was evaluated. From 56,098 evaluated studies, 133 studies could be further pursued. These supplied data concerning microfracturing, osteochondral autograft transfer system (OATS), ACI and MACI. The modified Coleman Methodical Score (CMS) and the level of evidence (LOE) were applied to evaluate the quality. In these studies, a total of 6,920 patients were reviewed with a median of 32 patients per study and a mean follow-up of 24 months. The mean CMS was 58 of 100 points. No study reached 100 points in the CMS. Three studies reached a level above 90; 10 studies were Level I; 5 studies reached Level II; 7

studies reached Level III; and 111 studies Level IV. Magnetic resonance imaging scans to verify the clinical data were used by only 72 studies. The means in the modified CMS for the different procedures were as follows: ACI 58 points, MACI 57 points, microfracturing 68 points and OATS 50 points. A total of 24 studies applied the Lysholm Score (LS) for clinical evaluation of cartilage surgery. All operative procedures yielded comparable improvements of the LS (nno-significant) meaning that no operative procedure proved superior. The authors concluded that as the majority of studies evaluated by this review is insufficient for evidence-based method purposes, more coherent studies with LOE of I or II are needed.

Ebert et al (2011) noted that the availability remains limited of mid-term clinical and radiological results into MACI. Outcomes are required to validate the efficacy of MACI as a suitable surgical treatment option for articular cartilage defects in the knee. A prospective evaluation was undertaken to assess clinical and MRI-based outcomes to 5 years in 41 patients (53 grafts) after MACI to the knee. After MACI surgery and a 12-week structured rehabilitation program, patients underwent clinical assessments (Knee injury and Osteoarthritis Outcome Score, SF-36, 6-minute walk test, knee range of motion) and MRI assessments at 3, 12, and 24 months, as well as 5 years after surgery. The MRI evaluation assessed 8 previously defined pertinent parameters of graft repair, as well as a combined MRI composite score. A significant improvement ($p < 0.05$) was demonstrated for all Knee injury and Osteoarthritis Outcome Score and SF-36 subscales over the post-operative timeline, as well as the 6-minute walk test and active knee extension. A significant improvement ($p < 0.0001$) was observed for the MRI composite score, as well as several individual graft scoring parameters. At 5 years after surgery, 67 % of MACI grafts demonstrated complete infill, whereas 89 % demonstrated good to excellent filling of the chondral defect. Patient demographics, cartilage defect parameters, and injury/surgery history demonstrated no significant pertinent correlations with clinical or MRI-based outcomes at 5 years, and no significant correlations existed between clinical and MRI-based outcome measures. At 5 years after surgery, 98 % of patients were satisfied with the ability of MACI surgery to relieve knee pain; 86 %, with improvement in their ability to perform normal daily tasks; and 73 %, with their ability to participate in sport 5 years after MACI. The authors concluded that these results suggest that

MACI provides a suitable mid-term treatment option for articular cartilage defects in the knee. Moreover , they stated that long-term follow-up is essential to confirm whether the repair tissue has the durability required to maintain long-term patient quality of life.

Dixon et al (2011) presented the functional outcomes of MACI for a single surgeon series in a general hospital setting. A total of 27 patients, mean age of 41, were reviewed at 3.7 (range of 1 to 5) years. Patients were assessed using the AOFAS hindfoot scale, Tegener activity score and University of California lower extremity activity scale. Magnetic resonance imaging findings were also reviewed. While most patients report a significant improvement in symptoms with full return to activities of daily living, 36 % of those under 40 and 78 % of those over 40 reported restricted recreational activity. Of the patients under 40 years of age, 86 % were able to run compared with 23 % of those over 40. Of patients over 40, 64 % continued to have moderate or severe pain. The authors concluded that careful pre-operative counseling is required for patients of all ages regarding likely outcomes. In patients over 40, the procedure is unlikely to give good pain relief and alternative options should be considered.

Schneider et al (2011) reported a prospective multi-center study of MACI of the knee using a new type I collagen hydrogel (CaReS). From 2003 to 2008, 116 patients (49 women and 67 men; mean age of 32.5 +/- 8.9 years) had CaReS implantation of the knee in 9 different centers. On the basis of the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package 2000, the International Knee Documentation Committee (IKDC) score, pain score (visual analog scale [VAS]), SF-36 score, overall treatment satisfaction and the IKDC functional status were evaluated. Patient follow-up was performed at 3, 6, and 12 months after surgery and annually thereafter. Mean follow-up was 30.2 +/- 17.4 months (range of 12 to 60 months). There were 67 defects of the medial condyle, 14 of the lateral, 22 of the patella/trochlea, and 3 of the tibial plateau, and 10 patients had 2 lesions. The mean defect size was 5.4 +/- 2.4 cm(2); 30 % of the defects were less than 4 cm(2) and 70 % were greater than 4 cm(2). The IKDC score improved significantly from 42.4 +/- 13.8 pre-operatively to 70.5 +/- 18.7 ($p < 0.001$) at latest follow-up. Global pain level significantly decreased ($p < 0.001$) from 6.7 +/- 2.2 pre-operatively to 3.2 +/- 3.1 at latest follow-up. There also was a

significant increase of both components of the SF-36 score. The overall treatment satisfaction was judged as very good or good in 88 % by the surgeon and 80 % by the patient. The IKDC functional knee status was grade I in 23.4 %, II in 56.3 %, III in 17.2 %, and IV in 3.1 % of the patients. The authors concluded that MACI employing the CaReS technology for the treatment of chondral or osteochondral defects of the knee is a safe and clinically effective treatment that yields significant functional improvement and improvement in pain level. However, they stated that further investigation is necessary to determine the long-term viability and clinical outcome of this procedure.

In a prospective, multi-center study, Enea et al (2012) evaluated (i) the quality of the repair tissue obtained from biopsies taken during second-look arthroscopy and (ii) the relationship between the histological outcome, the macroscopic appearance of the repair and functional status in patients who have undergone MACI for chondral defect repair. A total of 33 second-look core biopsies from 30 patients treated with MACI were analyzed. At the time of biopsy, the surgeon reported the reason for the second-look arthroscopy, the quality of the repair tissue and the patient's functional status on a standardized form. Biopsies together with patient data were sent to the authors' center to undergo blind histological evaluation and data analysis. The median overall ICRS II histological score of the examined population was 57 (1st to 3rd quartile 41 to 75). According to the ICRS cartilage repair assessment (CRA) arthroscopic evaluation, 10 biopsies (30 %) were classified as normal, 17 (51 %) as nearly normal, 4 (12 %) as abnormal and 2 (6 %) as severely abnormal. The histological outcome was not significantly related either to the macroscopic appearance of the lesion or to the patient's functional status at the time of biopsy. The authors concluded that in the examined population, the macroscopic appearance of the repair tissue gave an overly favorable impression in comparison with the real histological composition of the tissue, which was possibly still maturing in many cases. The healing process after MACI needs to be better understood through a larger histological study, and a longer follow-up is needed to better clarify the relationship between histology and long-term functional status.

Petri et al (2013) compared the CaReS(®) technique, which is a MACI technique, to microfracture for treating patello-femoral articular cartilage lesions. Between May 2003 and December 2005, a total 17 patients with an isolated patella-femoral cartilage defect (International Cartilage Repair Society III/IV) were treated with the CaReS(®) technique. After adjusting for inclusion and exclusion criteria, 10 of these patients could be included in this study; 10 patients treated with microfracture were chosen as a matched-pair group. Clinical outcome was evaluated 3 years after surgery by SF-36, International Knee Documentation Committee (IKDC) subjective evaluation of the knee, Lysholm Score, and Cincinnati Modified Rating Scale scores. Patients treated with CaReS(®) had statistically significantly improved IKDC, Lysholm, and Cincinnati scores 36 months after surgery compared with pre-operatively. When comparing outcome between groups 36 months after surgery, there was no statistically difference in IKDC, Lysholm, and Cincinnati scores. The authors concluded that this the first trial comparing the CaReS(®) technique and microfracture for treating patella-femoral articular cartilage lesions, and results show that CaReS(®) yielded comparable results to microfracture. The authors noted that the small number of patients is a limiting factor of the study, leading to results without statistical significance. They stated that a multi-centric prospective randomized study comparing the 2 procedures is desirable.

The FDA approved Maci (autologous cultured chondrocytes on porcine collagen membrane) (Vericel, Cambridge, MA) for the repair of symptomatic, full-thickness cartilage defects of the knee in adult patients (FDA, 2016). Maci is composed of a autologous cells that are expanded and placed onto a bio-resorbable porcine-derived collagen membrane that is implanted over the area where the defective or damaged tissue was removed. Each Maci implant consists of a small cellular sheet containing 500,000 to 1,000,000 cells per cm2. The amount of Maci administered depends on the size of the cartilage defect, and is trimmed to ensure that the damaged area is completely covered. Multiple implants may be used if there is more than one defect.

The FDA approval was supported by the results of SUMMIT trial (Superiority of MACI implant versus Microfracture Treatment in patients with symptomatic articular cartilage defects in the knee), a Phase 3 two-year, prospective, multicenter, randomized, open-label, parallel-group

study that enrolled a total of 144 patients, ages 18 to 54 years, with at least one symptomatic Outerbridge Grade III or IV focal cartilage defect on the medial femoral condyle, lateral femoral condyle, and/or the trochlea (Saris, et al., 2014; Vericel, 2016). The co-primary efficacy endpoint was change from baseline to Week 104 for the subject's Knee injury and Osteoarthritis Outcome Score (KOOS) in 2 subscales: Pain and Function (Sports and Recreational Activities [SRA]). At Week 104, KOOS pain and function (SRA) had improved from baseline in both treatment groups, but the improvement was statistically significantly ($p<0.001$) greater in the MACI group compared with the microfracture group. In a responder analysis, the proportion of subjects with at least a 10-point improvement in both KOOS pain and function (SRA) was greater in the MACI group (63/72 = 87.5%; 95% CI [77.6%, 94.6%]) compared with the microfracture group (49/72 = 68.1%; 95% CI [56.0%, 78.6%]). Patients from the two-year SUMMIT study had the option to enroll in a three-year follow-up study (extension study). A majority of the patients who completed the SUMMIT study also participated in a three year extension study. The FDA concluded that the overall efficacy data support a long-term clinical benefit from the use of the Maci implant in patients with cartilage defects of the knee.

The most frequently occurring adverse reactions (≥5%) reported for MACI in the 2-year randomized, controlled clinical trial were arthralgia, tendonitis, back pain, joint swelling, common cold-like symptoms, headache, and joint effusion. Serious adverse reactions reported for MACI were arthralgia, cartilage injury, meniscus injury, treatment failure, and osteoarthritis.

According to the manufacturer, Maci is expected to be a less tedious technical procedure performed via mini-arthrotomy (Vericel, 2016). The seeded cellular membrane is directly implanted to the defect area and secured by a fibrin sealant, which eliminates the need for suturing and testing of water tightness. The Maci procedure is quicker to perform and requires a smaller incision.

MACI is contraindicated in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin. MACI is also contraindicated for patients with severe osteoarthritis of the knee, inflammatory arthritis, inflammatory joint

disease, or uncorrected congenital blood coagulation disorders. MACI is also not indicated for use in patients who have undergone prior knee surgery in the past six months, excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant. MACI is contraindicated in patients who are unable to follow a physician-prescribed post-surgical rehabilitation program.

The safety of MACI in patients with malignancy in the area of cartilage biopsy or implant is unknown. Expansion of present malignant or dysplastic cells during the culturing process or implantation is possible.

Patients undergoing procedures associated with MACI are not routinely tested for transmissible infectious diseases. A cartilage biopsy and MACI implant may carry the risk of transmitting infectious diseases to healthcare providers handling the tissue. Universal precautions should be employed when handling the biopsy samples and the MACI product.

To create a favorable environment for healing, concomitant pathologies that include meniscal pathology, cruciate ligament instability and joint misalignment, must be addressed prior to or concurrent with the implantation of MACI.

Treatment guidelines regarding the use of thromboprophylaxis and antibiotic prophylaxis around orthopaedic surgery should be followed. Use in patients with local inflammations or active infections in the bone, joint, and surrounding soft tissue should be temporarily deferred until documented recovery.

The MACI implant is not recommended during pregnancy. For implantations post-pregnancy, the safety of breast feeding to infant has not been determined. Use of MACI in pediatric patients or patients over 55 years of age has not been assessed.

On December 13, 2016, the U.S. FDA announced the approval of MACI, an autologous cultured chondrocytes on porcine collagen membrane, for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee in adult patients. MACI is the first FDA-approved product that applies the process of tissue engineering to grow cells on scaffolds using healthy cartilage tissue from the patient’s own knee (FDA,

2016). Per Prescribing Information (Vericel, 2017), each 3 x 5 cm cellular sheet (MACI implant) consists of autologous cultured chondrocytes on a resorbable porcine Type I/III collagen membrane, at a density of at least 500,000 cells per cm2.

In 2017, Carticel, the first generation ACI, was replaced by MACI. Carticel is no longer marketed in the United States (Vericel, 2018).

Lenz and colleagues (2020) stated that MACI is an established treatment method for larger joints and has shown promising results in the ankle as well. In a case-series study, these researchers presented results of patients after ankle MACI with long-term follow-up of clinical and radiological outcomes. A total of 15 patients who underwent MACI grafting from August 2003 to February 2006 were included in this analysis. The mean follow-up was 12.9 years. Clinical evaluations were performed using the AOFAS, Foot and Ankle Activity Measurement (FAAM), and VAS scoring systems and MOCART scoring system for radiological evaluation. The mean size of the talar osteochondral defects was 204 mm2. These investigators found a significant improvement in mean AOFAS score from 60 pre-operatively to a mean of 84 at 12 years post-operatively. The 12-year FAAM score for ADL was 89 % (range of 62 % to 99 %). The mean 12-year MOCART score was 65 points (range of 30 to 100 points) with significant agreement between assessors ($p < 0.001$); however, the MOCART scores did not correlate with the FAAM scores ($p = 0.86$). The authors concluded that considering the long-term follow-up, they believed MACI is a reliable treatment method for talar osteochondral defects providing lasting pain relief and satisfying clinical results; however, with an equivalent outcome, but at higher costs, and the requirement for 2 operative procedures, the results did not appear to be superior to other established methods. The clinical utility of the MOCART score requires further scrutiny since these researchers were unable to show any correlation between the score and clinical outcome. Level of evidence = IV.

In a systematic review, Colombini et al (2023) examined the mid- and long-term effectiveness of ACI and MACI in the treatment of patients with knee cartilage defects in the presence of osteoarthritis. PubMed and Cochrane databases were systematically searched for studies describing the treatment of knee osteoarthritis with ACI or MACI (Kellgren-Lawrence

[KL] greater than or equal to 1, minimum follow-up of 36 months). Results were reported according to the PRISMA guidelines and included Lysholm, Western Ontario McMaster University and International Knee Documentation Committee scores. Of the 127 full-text articles assessed for eligibility, only 5 studies were selected based on inclusion/exclusion criteria (2 on ACI and 3 on MACI). In both groups, the defects were mainly located at femoral level, size 2.2 to 15.1 cm2 in the ACI and 2.0 to 7.6 cm2 in the MACI group. ACI was mostly used for patients affected by KL I, whereas MACI for patients with KL II to IV. The data obtained from 235 patients (161 ACI, 74 MACI) showed that ACI and MACI sustained stable clinical improvements up to 11 and 15 years, respectively, with a failure rate of about 10 % up to 11 years. Scarce biological details regarding chondrocyte implantation were reported. The authors concluded that ACI and MACI procedures for the treatment of knee cartilage lesions associated to OA showed long-term success and allowed delaying arthroplasty. Moreover, these researchers stated that further investigations reporting homogenous data and precise patient characterization are needed to carry out an effective literature meta-analysis, and identify the clinical relevance of these procedures. Level of Evidence = IV.

The authors stated that this systematic review had several drawbacks. First, the retrospective nature of most of the included studies carried the risk of selection bias. Given the lack of quantitative data, it was not possible to perform the statistical analyses including only prospective studies. Although the included studies were methodologically well conducted, most of them entailed a limited sample size. Second, the description of the diagnoses, eligibility criteria, and surgical procedures were overall satisfactory in most studies; however, information on rehabilitation protocols was seldom reported and often biased, and the timing of assessing outcome was often unclear. Between studies heterogeneities are evident. One study examined surgical procedures on patients with chondral defects, others combined patients with chondral and osteochondral injuries. The impact on the surgical outcome of adding a subchondral bone procedure to ACI was not fully clarified. Subchondral bone impairment is always present in OCD defects, but not so common following traumatic chondral injuries. One article focused exclusively on patients with OCD, and many investigators did not clearly state the etiology of the defects. Whether the etiology (OCD or trauma)

influences the clinical outcome was unclear; given the limited available data, no further subgroup analyses were possible. Third, the location of the defects was variable among the included studies: 1 study examined the patello-femoral joint, 2 studies assessed the femoral condyles, and 6 studies evaluated mixed locations. Most researchers carried out the interventions in combination with other procedures, or did not clearly state whether the procedures were performed in isolation. A resorbable collagen I/III porcine-derived membrane was used by most investigators. One author used 3D chondro-spheres (Spherox), which adhere directly to the subchondral bone without the need of a membrane to stabilize the implant. Two authors combined data of patients who underwent PACI and collagen membrane ACI (CACI), as they evolved their technique during the patient recruitment. Given the limited data available for inclusion, no further subgroup analyses were possible. Fourth, the IKDC and the KOOS questionnaires evaluate pain, symptoms, and function in daily life and sport activities, and are widely employed to evaluate patients with chondral defects of the knee. Previous studies showed their validity, reliability, and responsiveness in the adult population; however, the validity of IKDC and KOOS in skeletally immature patients is controversial; thus, the child friendly Pedi-IKDC and KOOS-Child were developed and validated. However, none of the included studies referred to the child friendly PROMs, and this represents a further bias; hence, these findings must be considered within the limitations of the present investigation. These investigators stated that future investigations should validate these results in a clinical setting.

In a case-series study, Eichinger et al (2024) examined mid-term (5 to 7 years) outcomes following MACI in the PF joint. A total of 26 patients who had undergone MACI using the Novocart 3D scaffold were evaluated. Clinical outcomes were determined by measuring the SF-36 and IKDC scores and the WOMAC values pre-operatively, and 3, 6, and 12 months, and a mean of 6 years post-operatively. At the final follow-up, the MOCART score was evaluated. A total of 22 patients with 23 focal cartilage defects (19 patella and 4 trochlea) were available for the final follow-up. The mean defect size was 4.0 ± 1.9 cm2 (range of 2.4 to 9.4 cm2). All clinical outcome scores improved significantly until 5 to 7 years after MACI (SF-36 score, 61.2 ± 19.6 to 83.2 ± 11.6; $p = 0.001$; IKDC score, 47.5 ± 20.6 to 74.7 ± 15.5; $p < 0.001$; and WOMAC, 29.8 ± 15.7 to 8.2 ± 10.3; $p < 0.001$). The mean MOCART score was 76.0 ± 11.0 at the

final follow-up; 19 of the 22 patients (86.4 %) were satisfied with the outcomes after 5 to 7 years and responded that they would undergo the procedure again. The authors concluded that MACI in the PF joint showed good mid-term clinical results with a significant reduction in pain, improvement in function, and high patient satisfaction. These clinical findings were supported by radiological evidence from MOCART scores. Level of Evidence = IV.

The authors stated that this study had several drawbacks. First, the cohort examined in this study was quite small (n = 22), similar to the cohorts in other reports of PF MACI, since a limited number of patients underwent the procedure. There was no control group. Second, as is typical in the surgery of the PF joint, this patient cohort needed a high number of concomitant procedures. This factor could potentially influence the outcomes and should be considered when interpreting the results. Third, this study population included both patellar as well as trochlear defects with a disproportionally a high number of patellar defects versus a low number of trochlear lesions. This imbalance could influence the generalizability of the results, especially regarding the applicability of these findings to trochlear defects. Fourth, no further clinical outcome scoring was carried out between the 1-year and final follow-up, which was a long time interval. Moreover, the patients started full sports activity 1 year after surgery; thus, a decreasing tendency in clinical outcomes before the final follow-up could not be fully excluded; however, such a tendency was very unlikely considering the findings reported in various other studies. Fifth, MRI was conducted only at the final follow-up, and no baseline MRI was carried out after surgery. However, the reported MOCART score at the final follow-up was comparable with the values obtained after 2 years of follow-up reported by Zak et al (2014) underlining the preservation of the reported cartilage tissue quality at mid-term follow-up.

Osteochondritis Dissecans (OCD)

Osteochondritis dissecans (OCD) is a type of osteochondritis in which articular cartilage and associated bone becomes partially to totally detached to form joint loose bodies. It affects mainly the knee, ankle and elbow joints.

Moriya et al (2007) investigated the biochemical properties, histological and immunohistochemical appearance, and magnetic resonance (MR) imaging findings of reparative cartilage after autologous chondrocyte implantation (ACI) for osteochondritis dissecans (OCD). The investigators found that reparative cartilage after ACI had less GAG concentration and was inferior to healthy hyaline cartilage in histological and immunohistochemical appearance and on MRI findings.

In a study of long-term outcomes of ACI in 31 patients (36 knees) assessed 9 to 18 years after treatment with autologous chondrocyte implantation ACI), Vasiliadis et al (2010) found evidence to show that violation of the subchondral bone before the ACI (either being an osteochondritis dissecans lesion a priori or having undergone a marrow-stimulating technique) increases the incidence of intralesional osteophytes. Intralesional osteophytes were in 64% of the lesions, mainly in younger patients with osteochondritis dissecans lesions or a history of subchondral bone surgeries.

Winthrop and colleagues (2015) noted that osteochondritis dissecans (OCD) of the knee is a disease of the sub-chondral bone with secondary injury to the overlying articular cartilage. OCD lesions are generally categorized as juvenile-growth plates open-or adult-growth plates closed. This maturity-based classification scheme has a prognostic value in that many juvenile OCD lesions will heal with conservative care while most symptomatic adult OCD lesions need surgical intervention. OCD can result in pain, knee joint effusions, loose body formation, and arthritis. Short-term treatment goals include pain and symptom resolution while the long-term goal is to minimize arthritis. Surgical options include debridement, drilling, micro-fracture, reduction and fixation, autograft osteochondral transplantation, autologous chondrocyte implantation (ACI), and allograft osteochondral transplantation.

Shaikh and associates (2015) stated that OCD of the knee is identified with increasing frequency in the adolescent patient. Left untreated, OCD can cause significant impairment and restriction in physical activity and development of osteoarthritis at an early age. The diagnosis of lesions of OCD can be confirmed on plain radiographs; magnetic resonance imaging (MRI) has emerged as the gold standard to evaluate the stability of the lesion and the integrity of the overlying articular cartilage.

Treatment of OCD lesions depend on the stability of the lesion. Stable lesions can be treated conservatively by physical activity modification and immobilization. Unstable lesions and stable lesions not responding to conservative measures should be treated surgically. Surgical options range from arthroscopic drilling, either trans-articular or extra-articular drilling for stable lesions or salvage procedures such as autologous chondrocyte transplantation (ACT), mosaicplasty to restore joint and cartilage congruency.

Peterson et al (2003) reported on a retrospective case series on the intermediate to long-term results of ACI in patients with osteochondritis dissecans. Fifty-eight patients with radiographically documented osteochondritis dissecans of the knee underwent treatment with ACI between 1987 and 2000 and were assessed clinically with use of standard rating scales. Twenty-two patients consented to arthroscopic second-look evaluation of graft integrity. The mean age of the patients at the time of ACI was 26.4 years (range, fourteen to fifty-two years). Seven patients were less than eighteen years old. Thirty-five patients (60%) had juvenile-onset disease, and forty-eight patients (83%) had had a mean of 2.1 prior operations. The defect was located on the medial femoral condyle in thirty-nine patients and on the lateral femoral condyle in nineteen. The mean lesion size was 5.7 cm (2) (range, 1.5 to 12.0 cm (2)), and the mean defect depth was 7.8 mm (range, 4 to 15 mm). After a mean duration of follow-up of 5.6 years, 91% of the patients had a good or excellent overall rating on the basis of a clinician evaluation and 93% had improvement on a patient self-assessment questionnaire. The Tegner-Wallgren, Lysholm, and Brittberg-Peterson VAS scores were all improved. The macroscopic quality of graft integrity averaged 11.2 on a 12-point scale, with only one graft having a score of <9 points. Two patients had a failure of treatment in the early postoperative period. Only one patient who had had a good or excellent rating at two years had a decline in clinical status at the time of the latest follow-up.

Micheli et al (2006) reported on a registry study of 37 patients who were treated with ACI before the age of 18 years. Patient-rated assessments of overall condition, pain, and swelling were measured using modified, 10-point scales of the Cincinnati Knee Rating System.: Mean age was 16 years (11Y17); 22 boys and 15 girls. Twenty-three patients underwent at least 1 cartilage repair procedure before the cartilage harvest, including

11 who had a marrow stimulation procedure. Fourteen patients were diagnosed with osteochondritis dessicans lesions. Thirty-five patients had single defects (mean size, 5.4 cm2). Thirty-two patients completed self-evaluations at a minimum of 2 years after implantation (mean follow-up = 4.3 years). The mean change in scale scores measuring overall condition, pain, and swelling were 3.8, 4.1, and 3.4 points, respectively. One patient had an implantation that failed.

Cole et al (2012) reported on a case series analysis of the Study of the Treatment of Articular Repair (STAR) to evaluate the effectiveness of autologous chondrocyte implantation (ACI) in a subset of adult patients with osteochondritis dissecans (OCD) knee lesions. Forty patients with at least one failed non-ACI treatment for an OCD knee lesion received ACI in a multicenter study. The modified Cincinnati Knee Rating System, the Knee injury and Osteoarthritis Outcome Score (KOOS), and the Short-Form 36 Health Survey (SF-36) were used to assess patient outcomes at baseline and periodically to 48 months. Treatment failures, serious adverse events, and subsequent surgical procedures were recorded. Thirty-two (80%) patients completed the 48-month study. Autologous chondrocyte implantation treatment was successful in 85% of patients. Mean (6 standard deviation) overall knee condition score (modified Cincinnati) was 3.1 6 1.1 at baseline and 6.8 6 2.0 at month 48. Clinically and statistically significant (P\.001) mean improvements from baseline to month 48 for the KOOS were as follows: 51.5 to 79.5 (pain), 54.8 to 77.9 (symptoms), 27.5 to 63.6 (sports and recreation ability), 63.5 to 86.7 (activities of daily living), and 21.9 to 59.6 (knee-related quality of life). The mean improvement (P\.001) in overall health assessed by the SF-36 was 35.4 to 45.5. Thirty-five percent (n = 14/40) of patients had a subsequent surgical procedure, most frequently debridement of the cartilage lesion. Treatment failure occurred in 6 of 32 (19%) patients.

Martincic et al (2014) reported on a case series assessing the 10-year clinical outcomes of periosteum ACI due to cartilage lesions of the femoral condyles. Thirty-three of 45 patients (3 failures, 7 nonresponders, 2 others) were available for clinical and radiographic evaluation at 2, 5, and 10 years. Patients were categorized into groups with focal cartilage lesions (n = 11), osteochondritis dissecans (OCD) (n = 12), and cartilage lesions with simultaneous ACL reconstruction (ACL) (n = 10). Seven patients in the overall series required an arthroscopic re-intervention (3

ACI related, 4 ACI unrelated). Subjective knee scores and activity scores were significantly improved at 2 years toward their pre-operative levels and then remained stable up to 10 years; however, patients did not reach their pre-injury activity levels. Upon 10-year examination, using the IKDC knee examination form, there were 15 normal, 11 nearly normal, 5 abnormal, and 2 severely abnormal knees. Radiographic evidence of osteoarthritis was found in 45 % of patients (5 focal lesions, 2 OCD, and 8 ACL).

Pascual-Garrido et al (2009b) reported on the outcomes of a variety of surgical procedures in a cohort of adults with OCD. The cohort included 46 adult patients (48 knees) with adult OCD of the knee who had undergone surgical treatment (debridement, drilling, loose-body removal, arthroscopic reduction and internal fixation, microfracture, osteochondral allograft, or autologous chondrocyte implantation). The average patient age was 34 6 9.5 years (range, 20-49) and patients were followed for 4.0 6 1.8 years. The mean defect size was 4.5 6 2.7 cm2. Outcomes were assessed via clinical assessment and established outcome scales, including the Lysholm, International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Tegner, Cincinnati, and Short Form-12. Statistically significant improvement (P\.05) was noted in all outcome scales, including Noyes, Tegner, Lysholm, IKDC, KOOS (subdivided into 5 categories including Pain, Symptoms, Activities of Daily Living, Sport, and Quality of Life), Short Form-12 Physical, and Short Form-12 Mental. Seven knees (14%) had clinical failure of the initial treatment and underwent a revision procedure at a mean follow-up of 14 months. Patients treated with arthroscopic reduction and internal fixation and loose-body removal demonstrated a statistically higher postoperative percentage score increase for the KOOS Sport (P 5 .008) and KOOS Quality of Life (P 5 .03) categories than those treated with an osteochondral allograft. Outcomes of ACI could not be compared with other surgical procedures in this cohort because there was insufficient power (only three subjects received ACI in this cohort).

Vijayan et al (2014) reported on the results in patients who underwent revision cartilage transplantation of their original ACI/MACI graft for clinical or graft-related failure. The investigators assessed 22 patients (12 men and 10 women) with a mean age of 37.4 years (18 to 48) at a mean of 5.4 years (1.3 to 10.9). Four of the 22 patients had OCD. The mean

period between primary and revision grafting was 46.1 months (7 to 89). The mean defect size was 446.6 mm2 (150 to 875) and they were located on 11 medial and two lateral femoral condyles, eight patellae and one trochlea. The mean modified Cincinnati knee score improved from 40.5 (16 to 77) pre-operatively to 64.9 (8 to 94) at their most recent review ($p < 0.001$). The visual analogue pain score improved from 6.1 (3 to 9) to 4.7 (0 to 10) ($p = 0.042$). A total of 14 patients (63%) reported an 'excellent' (n = 6) or 'good' (n = 8) clinical outcome, 5 'fair' and one 'poor' outcome. Two patients underwent patellofemoral joint replacement.

ACI has been combined with bone plugs in OCD. Bhattacharjee and co-workers (2016) noted that structural and functional outcome of bone graft with 1st- or 2nd-generation ACI in treating cartilage and sub-chondral bone defect has not been reported previously. In a case-series study, these researchers evaluated the outcome of simultaneous transplantation of an autologous bone plug with 1st- or 2nd-generation ACI for restoration of concomitant sub-chondral bone and full-thickness cartilage defect in the femoral condyle of the knee. A total of 17 patients (mean ± SD age of 27 ± 7 years; range of 17 to 40; 12 with OCD (International Cartilage Repair Society [ICRS] grades 3 and 4) and 5 with an isolated osteochondral defect (ICRS grade 4) had the defect reconstructed with implantation of a uni-cortical autologous bone graft combined with ACI (the OsPlug technique). Functional outcome was assessed with Lysholm scores obtained pre-operatively and at 1 and 5 years post-operatively. The repair site was evaluated with the Oswestry Arthroscopy Score (OAS), MOCART score (MRI observation of cartilage repair tissue), and ICRS II histology score. Formation of a sub-chondral lamina and lateral integration of the bone grafts were evaluated from MRI scans. The mean defect size was 4.5 ± 2.6 cm(2) (range of 1 to 9 cm(2)), and the mean depth was 11.3 ± 5 mm (range of 5 to 18). The pre-operative Lysholm score improved from 45 (interquartile range [IQR], 24; range of 16 to 79) to 77 (IQR, 28; range of 41 to 100) at 1 year ($p = 0.001$) and 70 (IQR, 35; range of 33 to 91) at 5 years ($p = 0.009$). The mean OAS of the repair site was 6.2 (range of 0 to 9) at a mean of 1.3 years. The mean MOCART score was 61 ± 22 (range of 20 to 85) at 2.6 ± 1.8 years. Histology demonstrated generally good integration of the repair cartilage with the underlying bone. Poor lateral integration of the bone graft, as assessed on MRI scan, and a low OAS were significantly associated with a poor Lysholm score and failure. A total of 3 patients had treatment

failure, with 1 requiring total knee replacement at 5 years (Lysholm score of 33 at failure) and the other 2 requiring further surgical intervention because of persistent symptoms at 2 and 4 years, respectively (both had Lysholm score of 45 at failure). The Lysholm score in these patients before failure were still noted to be higher than at the pre-operative level. The authors concluded that the OsPlug technique showed significant improvement of functional outcome for up to 5 years in patients with high-grade OCD or osteochondral defect. This was the 1st report describing association of bone graft integration with functional outcome after such a procedure. It also demonstrated histologic evidence of integration of the repair cartilage with the underlying bone graft.

There is emerging evidence for MACI as a treatment for OCD lesions. Ochs et al (2011) implemented a novel 1-step surgical procedure for OCD treatment consisting of MACI and simultaneous bone reconstruction including the subchondral lamina. The investigators reported on a small retrospective case series of 2-to 5-year results of this technique, assessing correlations of clinical function and cartilage and bone remodeling processes. Twenty-six patients with symptomatic condylar knee OCD (International Cartilage Repair Society OCD III/IV) were treated with MACI and monocortical cancellous cylinders for defect filling and subchondral bone plate reconstruction using cortical graft layers as novel subchondral lamina. Evaluations were performed with clinical rating scales and 1.5-T magnetic resonance imaging using the magnetic resonance observation of cartilage repair tissue (MOCART) score and a newly implemented subchondral lamina remodeling grade. The defect size was 5.3 ± 2.3 cm(2). The defect depth was 8.7 ± 2.4 mm. After a follow-up of 39.8 ± 12.0 months, all scores improved significantly. Nineteen patients (73%) reached good/excellent results in the Lysholm-Gillquist score (preoperatively: 53.2 ± 18.0 points; latest follow-up: 88.5 ± 9.5 points) and the Cincinnati knee rating score (preoperatively: 51.7 ± 13.0 points; latest follow-up: 84.6 ± 11.7 points) and significant improvements in the subjective International Knee Documentation Committee (IKDC) score by 27.9% (preoperatively: 50.5% ± 16.1%; latest follow-up: 78.4% ± 13.4%). The MOCART score reached 62.4 ± 18.9 points. The clinical improvement and tissue remodeling occurred simultaneously and timed; thus, the cartilage defect filling and the lamina remodeling grades correlated significantly with each other, the follow-up time, and almost all clinical scores.

Vijayan et al (2012) reported on the results of 14 patients who underwent MACI with a mean follow-up of 5.2 years (2 to 8). There were 12 men and two women with a mean age of 23.6 years (16 to 40). The articular defects resulted from OCD in six and trauma in eight. The mean size of the defect was 7.2 cm2 (5.2 to 12 cm2) and were located on the medial (ten) or lateral (four) femoral condyles. The mean modified Cincinnati knee score improved from 45.1 (22 to 70) pre-operatively to 82.8 (34 to 98) at the most recent review ($p < 0.05$). The visual analogue pain score improved from 7.3 (4 to 10) to 1.7 (0 to 6) ($p < 0.05$). Twelve patients were considered to have a good or excellent clinical outcome. One graft failed at six years.

Filardo et al (2012) analysed the clinical outcome obtained with arthroscopic second generation autologous chondrocyte implantation (ACI) involving the arthroscopic implant of the bioengineered tissue Hyalograft C associated with bone grafting for the treatment of knee osteochondritis dissecans (OCD) at medium term follow-up. Thirty-four knees affected by symptomatic OCD grade III or IV on the ICRS (International Cartilage Repair Society) scale were treated and prospectively evaluated at 12, 24 months of follow-up, and at a final mean 6±1 years of follow-up. The mean age at treatment was 21±6 years. The average size of the defects was 3±1 cm2. Patients were evaluated with IKDC, EQ-VAS, and Tegner scores. A statistically significant improvement in all scores was observed after the treatment. The IKDC subjective score improved from 38±13 to 81±20, and 91% of the knees were rated as normal or nearly normal in the objective IKDC at the final evaluation. EQ-VAS and Tegner scores showed a statistically significant linear trend of improvement over time passing from 52±18 to 83±14 and from 2±1 to 5±3, respectively, at 6 years' follow-up. A better outcome was obtained in men, sport active patients, and smaller lesions. The authors stated that further studies are needed to confirm the results over time, and determine if there is only a symptomatic improvement, or if this procedure may also reinstate correct knee biomechanics and homeostasis, thus preventing or delaying knee degeneration.

Pestka et al (2012) examined if ACI used as a second-line treatment after failed arthroscopic microfracturing is associated with a higher failure rate and inferior clinical results compared with ACI as a first-line treatment. A total of 28 patients with isolated cartilage defects at the knee joint were

treated with ACI after microfracture as a first-line treatment had failed (failure defined as the necessity of re-intervention). These patients were assigned to group A and compared with a matched-pair cohort of patients of identical age, defect size, and defect location (group B) in which ACI was used as a first-line treatment. Failure rates in both groups were assessed. Post-operative knee status was evaluated with the IKDC score and Knee injury and Osteoarthritis Outcome Score (KOOS), and sporting activity was assessed by use of the Activity Rating Scale. Mean follow-up times were 48.0 months (range of 15.1 to 75.1 months) in group A and 41.4 months (range of 15.4 to 83.6 months) in group B. Differences between groups A and B were analyzed by Student's t-test. Group A had significantly greater failure rates (7 of 28 patients) in comparison with group B (1 of 28 patients; p = 0.0241). Mean (SD) post-operative IKDC scores revealed 58.4 (22.4) points in group A with a trend toward higher score results (69.0 [19.1] points) for patients in group B (p = 0.0583). Significantly different results were obtained for KOOS pain and activity of daily living subscales, whereas the remaining KOOS subscales did not show significant differences. Despite the significantly higher failure rate observed in group A, those patients did not participate in fewer activities or perform physical activity less frequently or at a lower intensity. The authors conclude that autologous chondrocyte implantation after failed microfracturing appears to be associated with a significantly higher failure rate and inferior clinical outcome when compared with ACI as a first-line treatment.

Jordan et al (2012) performed a systematic review of clinical outcomes following various treatments for chondral lesions of the hip and defined the techniques for the treatment of these cartilage defects. The full manuscripts of 15 studies were reviewed for this systematic review including case studies, case series, and clinical studies. A variety of techniques have been reported for the treatment of symptomatic chondral lesions in the hip. Microfracture, cartilage repair, ACI, mosaicplasty, and osteochondral allografting have all been used in very limited case series. Although good results have been reported, most studies lacked both a control group and a large number of patients. The authors concluded that the findings in this article do provide a good foundation for treatments and stimulant for further study in an inherently difficult to treat young patient population with articular cartilage defects in the hip.

Gross et al (2012) conducted a systematic review of clinical outcomes after cartilage restorative and reparative procedures in the glenohumeral joint, identified prognostic factors that predict clinical outcomes, provided treatment recommendations based on the best available evidence, and high-lighted literature gaps that require future research. These investigators searched Medline (1948 to week 1 of February 2012) and Embase (1980 to week 5 of 2012) for studies evaluating the results of arthroscopic debridement, microfracture, osteochondral autograft or allograft transplants, and ACI for glenohumeral chondral lesions. Other inclusion criteria included minimum 8 months' follow-up. The Oxford Level of Evidence Guidelines and Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations were used to rate the quality of evidence and to make treatment recommendations. A total of 12 articles met inclusion criteria, which resulted in a total of 315 patients; 6 articles pertained to arthroscopic debridement (n = 249), 3 to microfracture (n = 47), 2 to osteochondral autograft transplantation (n = 15), and 1 to ACI (n = 5). Whereas most studies reported favorable results, sample heterogeneity and differences in the use of functional and radiographic outcomes precluded a meta-analysis. Several positive and negative prognostic factors were identified. All of the eligible studies were observational, retrospective case series without control groups; the quality of evidence available for the use of the afore-mentioned procedures was considered "very low" and "any estimate of effect is very uncertain". The authors concluded that more research is needed to determine which treatment for chondral pathology in the shoulder provides the best long-term outcomes. They encouraged centers to establish the necessary alliances to conduct blinded, randomized clinical trials and prospective, comparative cohort studies necessary to rigorously determine which treatments result in the most optimal outcomes. At this time, high-quality evidence is lacking to make strong recommendations, and decision making in this patient population is performed on a case-by-case basis.

El Bitar et al (2014) noted that management of injuries to the articular cartilage is complex and challenging; it becomes especially problematic in weight-bearing joints such as the hip. Several causes of articular cartilage damage have been described, including trauma, labral tears, and femoro-acetabular impingement, among others. Because articular cartilage has little capacity for healing, non-surgical management options

are limited. Surgical options include total hip arthroplasty, microfracture, articular cartilage repair, ACI, mosaicplasty, and OAT. The authors concluded that advances in hip arthroscopy have broadened the spectrum of tools available for diagnosis and management of chondral damage; however, the literature is still not sufficiently robust to draw firm conclusions regarding best practices for chondral defects. Moreover, they stated that additional research is needed to expand the knowledge of and develop guidelines for management of chondral injuries of the hip.

Harris et al (2010) examined if (i) the current literature supports the choice of using autologous chondrocyte implantation (ACI) over other cartilage procedures with regard to clinical outcome, magnetic resonance imaging, arthroscopic assessment, and durability of treatment, (ii) the current literature supports the use of a specific generation of ACI, and (iii) there are patient-specific and defect-specific factors that influence outcomes after ACI in comparison with other cartilage repair or restoration procedures. These researchers conducted a systematic review of multiple databases in which they evaluated Level-I and II studies comparing ACI with another cartilage repair or restoration technique as well as comparative intergenerational studies of ACI. The methodological quality of studies was evaluated with use of Delphi list and modified Coleman methodology scores. Effect size analysis was performed for all outcome measures. A total of 13 studies (917 subjects) were included. Study methodological quality improved with later publication dates. The mean modified Coleman methodology score was 54 (of 100). Patients underwent ACI (n = 604), microfracture (n = 271), or osteochondral autograft (n = 42). All surgical techniques demonstrated improvement in comparison with the pre-operative status; 3 of 7 studies showed better clinical outcomes after ACI in comparison with microfracture after 1 to 3 years of follow-up, whereas 1 study showed better outcomes 2 years after microfracture and 3other studies showed no difference in these treatments after 1 to 5 years. Clinical outcomes after microfracture deteriorated after 18 to 24 months (in 3 of 7 studies). Autologous chondrocyte implantation and osteochondral autograft demonstrated equivalent short-term clinical outcomes, although there was more rapid improvement after osteochondral autograft (2 studies). Although outcomes were equivalent between 1st and 2nd-generation ACI and between open and arthroscopic ACI, complication rates were higher

with open, periosteal-cover, 1st-generation ACI (4studies). Younger patients with a shorter pre-operative duration of symptoms and fewer prior surgical procedures had the best outcomes after both ACI and microfracture. A defect size of greater than 4 cm(2) was the only factor predictive of better outcomes when ACI was compared with a non-ACI surgical technique. The authors concluded that cartilage repair or restoration in the knee provided short-term success with microfracture, ACI, or osteochondral autograft. There were patient-specific and defect-specific factors that influence clinical outcomes. Moreover, the authors stated that "To truly assess the efficacy and durability of autologous chondrocyte implantation in comparison with other techniques, future studies should attempt to limit the deficiencies mentioned within our discussion via proper and transparent subject enrollment with clearly stated inclusion and exclusion criteria; proper independently performed randomization techniques; no concurrent surgical interventions (anterior cruciate ligament reconstruction, realignment osteotomy, meniscal surgery, etc.); consistent surgical technique; longer clinical follow-up with an independent observer; the use of validated, responsive, and reliable outcome measures; and clear reporting of data with a statement of both clinical relevance and significance, as the two are not always coincident".

An UpToDate review on "Surgical therapy of osteoarthritis" (Kalunian, 2014) states that "Replacing localized regions of degenerated cartilage with autologous chondrocyte grafts has not been studied in large groups of patients. It is unlikely that this technique will be helpful in patients with advanced joint degeneration because of the large surface area that needs grafting in this setting. Most patients treated have been younger people with chondral defects caused by trauma …. Replacing localized regions of degenerated cartilage with autologous chondrocyte grafts may be beneficial for selected patients with less severe, localized articular cartilage defects, but it requires further study".

Schmidt et al (2014) reviewed the literature relative to muscle performance, knee joint biomechanics, and performance-based functional outcomes following articular cartilage repair and restoration surgical procedures in the knee. The online databases of PubMed (MEDLINE), CINAHL, SPORTDiscus, and Scopus were searched (inception to September 2013). Studies pertaining to muscle performance, knee joint biomechanics, and performance-based measures of function following

articular cartilage procedure in the knee were included. A total of 16 articles met the specified inclusion criteria; 7 studies evaluated muscle performance, all showing persistent deficits in quadriceps femoris muscle strength for up to 7 years post-procedure. Quadriceps femoris strength deficits of greater than 20 % were noted in 33 % and 26 % of individuals at 1 and 2 years following microfracture and ACI, respectively. Two studies evaluated knee mechanics post-ACI, showing persistent deficits in knee kinematics and kinetics for up to 12 months post-procedure compared to uninjured individuals. Seven studies showed improved functional capacity (6-minute walk test) over time, and 3 studies showed persistent performance deficits during higher-level activities (single-leg hop test) for up to 6 years post-procedure. Five studies comparing weight-bearing protocols (accelerated versus traditional/current practice) following ACI found few differences between the groups in function and gait mechanics; however, persistent gait alterations were observed in both groups compared to uninjured individuals. The authors concluded that significant quadriceps femoris strength deficits, gait deviations, and functional deficits persist for 5 to 7 years following ACI and microfracture surgical procedures. They stated that future research regarding rehabilitation interventions to help mitigate these deficits is warranted.

Oussedik et al (2015) performed a systematic review of the treatment of articular cartilage lesions of the knee by microfracture or ACI to determine the differences in patient outcomes after these procedures. These investigators searched PubMed/Medline, Embase, and The Cochrane Library databases in the period from January 10 through January 20, 2013, and included 34 articles in this qualitative analysis. All studies showed improvement in outcome scores in comparison with baseline values, regardless of the treatment modality. The heterogeneity of the results presented in the studies precluded a meta-analysis. The authors concluded that microfracture appeared to be effective in smaller lesions and is usually associated with a greater proportion of fibrocartilage production, which may have an effect on durability and eventual failure. Autologous chondrocyte implantation is an effective treatment that may result in a greater proportion of hyaline-like tissue at the repair site, which may in turn have a beneficial effect on durability and failure; it appears to be effective in larger lesions. Autologous chondrocyte implantation with periosteum has been shown to be associated with symptomatic cartilage hypertrophy more frequently than ACI with collagen membrane. Matrix-

associated ACI is technically less challenging than the other techniques available, and in lesions greater than 4 cm(2), it has been shown to be more effective than microfracture.

In a systematic review, Samsudin and Kamarul (2015) evaluated the current evidence for ACI generations relative to other treatment modalities, different cell delivery methods and different cell source application. Literature search was performed to identify all level I and II studies reporting the clinical and structural outcome of any ACI generation in human knees using the following medical electronic databases: PubMed, EMBASE, Cochrane Library, CINAHL, SPORTDiscus and NICE healthcare database. The level of evidence, sample size calculation and risk of bias were determined for all included studies to enable quality assessment. A total of 20 studies were included in the analysis, reporting on a total of 1,094 patients. Of the 20 studies, 13 compared ACI with other treatment modalities, 7 compared different ACI cell delivery methods, and 1 compared different cell source for implantation. Studies included were heterogeneous in baseline design, preventing meta-analysis. Data showed a trend towards similar outcomes when comparing ACI generations with other repair techniques and when comparing different cell delivery methods and cell source selection. Majority of the studies (80 %) were level II evidence, and overall the quality of studies can be rated as average to low, with the absence of power analysis in 65 % studies. The authors concluded that at present, there are insufficient data to conclude any superiority of ACI techniques. Considering its 2-stage operation and cost, it may be appropriate to reserve ACI for patients with larger defects or those who have had inadequate response to other repair procedures until hard evidence enables specific clinical recommendations be made.

In a retrospective study, Paatela and colleagues (2021) compared the clinical outcome of cartilage repair with (ACI in patients with OCD lesions and full-thickness cartilage lesions. This trial included a cohort of 115 consecutive patients with a cartilage lesion of the knee treated with ACI. Of the patients, 35 had an OCD lesion and 80 a full-thickness cartilage lesion. During a follow-up period from 2 to 13 years all treatment failures were identified. The failure rate between OCD lesions and full-thickness cartilage lesions was compared with Kaplan-Meier analysis. Patient-reported outcome was evaluated 2 years post-operatively with the

Lysholm score. During the follow-up 21 out of 115 patients encountered a treatment failure. The failure rate for full-thickness cartilage lesions was 19.1 % and for OCD lesions 43.3 % over the 10-year follow-up. Patient-reported outcome improved from baseline to 2 years post-operatively. The improvement from baseline was statistically significant, and the Lysholm score improved more than the minimal clinically important difference. The patient-reported outcome showed no difference between lesion types at 2 years. The authors concluded that the failure rate of 1st-generation ACI was higher in OCD lesions than in large full-thickness cartilage lesions, suggesting that OCD lesions may be associated with properties that affect the durability of repair tissue. Moreover, these researchers stated that future prospective studies are needed to ascertain how best to repair OCD lesions with biological tissue engineering.

Cartilage Defect in Rheumatoid Arthritis

Takahashi and Ishiguro (2015) noted that persistent inflammation in rheumatoid arthritis (RA) can lead to the profound degradation and defect of articular cartilage. These researchers stated that one can treat or induce the regeneration for the partial cartilage defect using the ACI or the matrix-assisted ACI. However, these regenerative methods cannot be applicable for the large size defect due to their limitation of the formable size or available cell numbers. The cell sheet technology or the intra-articular injection technique using the mesenchymal stem cells or the induced pluripotent stem cells (iPS cells) could be applied for the large size cartilage defect in RA patients in the future after additional studies.

Combination of Autologous Chondrocyte Implantation (ACI) and Osteochondral Autograft Transfer System

Duif et al (2015) stated that modern orthopedic surgery provides a variety of techniques for cartilage repair. Despite comprehensive scientific data about the single procedures, there is little experience with the combination of these methods. These investigators performed a PubMed-based literature search regarding the combination of cartilage restoration principles. The literature search was performed using the terms: "mosaicplasty" or "osteochondral transplantation" or "OATS" and "autologous chondrocyte implantation" or "autologous chondrocyte

transplantation" or "ACI" or "matrix-associated autologous chondrocyte implantation" or "MACI" and "combination". Abstracts were revised for relevance to this case. Additionally, these researchers presented a case report of the combinatory use of 3 established techniques. Two relevant publications, both reporting satisfying results concerning post-operative functional outcome, were found. These findings confirmed this first encouraging assessment, although statistically valid data and prospective studies are still missing. The authors concluded that simultaneous use of different techniques for cartilage repair may provide alternative operative solutions for single complex cases, although further studies are needed for a general recommendation.

Autologous Chondrocyte Implantation "Sandwich" Technique for Deep Osteochondral Lesions in the Knee

Minas and colleagues (2018) noted that treating symptomatic osteochondral defects is challenging, especially in young adults with deep (greater than 8 to 10 mm) empty defects after OCD or collapsed condyles secondary to avascular necrosis (AVN). For this population, osteoarthritis is inevitable if articular congruence is not restored. In a cohort study, these researchers described the ACI "sandwich" technique with autologous bone grafting (ABG) and compared it with ABG alone for restoration of the osteochondral unit. The mid-term to long-term outcomes in patients after the treatment for OCD and AVN were reported and compared. The outcomes for a consecutive cohort of 24 patients who underwent combined ABG with the ACI sandwich technique between 2001 and 2013 (ACI sandwich group) was compared with a historical control group of 17 consecutive patients who underwent ABG alone between 1995 and 2002 (ABG group) by a single surgeon for symptomatic deep (greater than 8 mm) osteochondral lesions. Patients who were followed-up with a minimum of 2 years were included in this study. The modified Cincinnati Knee Rating System, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a VAS, the Short Form-36, and a patient satisfaction survey were used to evaluate clinical outcomes. Survival analysis was performed using the Kaplan-Meier method, with no clinical improvement, graft failure, or conversion to prosthetic arthroplasty as the end-point (failure). Kellgren-Lawrence (K-L) grading to assess OA progression was also performed. In the ABG group, 13 of 17 patients (76 %) were available with a mean follow-up of

15.7 years post-operatively (range of 5 to 21 years). In the ACI sandwich group, all 24 patients were available with a mean follow-up of 7.8 years post-operatively (range of 2 to 15 years). No significant differences were observed between the groups in terms of age, sex, side of the operated knee, BMI, lesion type, lesion size, lesion depth, lesion location, or the need for re-alignment osteotomy; 8 patients (62 %) were considered failures in the ABG group, while 3 patients (13 %) were considered failures in the ACI sandwich group. The survival rate was significantly better in the ACI sandwich group than the ABG group (87 % versus 54 % at 5 years, respectively; p = 0.0025). All functional scores in patients with retained grafts significantly improved in the ACI sandwich group, whereas only the VAS score showed significant improvement in the ABG group. The patient satisfaction survey showed a very high satisfaction rate in the ACI sandwich group, with over 90 % of patients reporting their knees as good or excellent and being satisfied with the procedure. In the ACI sandwich group, K-L grading demonstrated no significant OA progression from pre-operatively to a mean 5.1 years post-operatively. The authors concluded that this study showed that the ACI sandwich technique provided excellent and superior survival rates compared to ABG alone and significant improvements over mid-term to long-term follow-up. This unique treatment offered native joint preservation for conditions that naturally will progress to OA and eventually require prosthetic arthroplasty.

The authors stated that this study had several drawbacks. First, these researchers did not have an empty defect group as a control. However, given that the patients were resistant to non-operative treatment with disabling symptoms before surgery, it was unacceptable to not offer them a surgical treatment. Second, this study set the ABG group as a historical control and was not a randomized study. However, the baseline patient and defect demographics were comparable. Third, some patients were lost to follow-up in the ABG group (2 were deceased, and 2 were lost to follow-up), although these investigators had a relatively high and acceptable follow-up rate (76 %). Fourth, 7 patients who underwent ABG alone were considered as failures when they were salvaged by ACI, as their symptoms remained unacceptable by ABG alone. Although this decision was made based on the clinical symptoms, MRI, and arthroscopic surgery, it possibly introduced an observer bias. Fifth, the length of follow-up was different substantially in the 2 groups, although

these researchers tried to mitigate it by performing Kaplan-Meier analysis. Finally, the authors were unable to review all the radiographs because of the conversion to digital films over the 20 years of this study. However, as other studies failed to report a radiographic follow-up, they believed that even a limited number of radiographs available could offer important information about OA prevention.

Matrix-Induced Autologous Chondrocyte Implantation (MACI) for Large Talar Osteochondral Defects

Ng and associates (2017) noted that repair of osteochondral lesions (OLT) of the talus can be difficult. Smaller lesions respond well to simple arthroscopy and microfracture, whereas larger cystic lesions may require allograft talus replacement or ankle fusions. The lesions in between are more difficult to treat. Autologous chondrocyte implantation and MACI have shown promising results. The authors stated that future research may include new techniques, pharmacologic intervention, and cell-based therapies, and may be better served with prospective observational studies instead of costly randomized controlled studies.

Erickson and colleagues (2018) stated that talar OLT occur frequently in ankle sprains and fractures. These researchers hypothesized that MACI will have a low re-operation rate and high patient satisfaction rate in treating OLT less than 2.5 cm2. A systematic review was registered with PROSPERO and performed with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using 3 publicly available free databases. Clinical outcome investigations reporting OLT outcomes with levels of evidence I to IV were eligible for inclusion. All study, subject, and surgical technique demographics were analyzed and compared. Statistics were calculated using Student's t-tests, 1-way ANOVA, Chi-squared, and 2-proportion Z-tests. A total of 19 articles met inclusion criteria, which resulted in a total of 343 patients; 6 studies pertained to arthroscopic MACI, 8 to open MACI, and 5 studies to open periosteal ACI (PACI). All studies were Level IV evidence. Due to study quality, imprecise and sparse data, and potential for reporting bias, the quality of evidence was low. In comparison of open and arthroscopic MACI, these investigators found both advantages favoring open MACI. However, open MACI had higher complication rates. The authors concluded that no procedure demonstrated superiority or inferiority

between the combination of open or arthroscopic MACI and PACI in the management of OLT less than 2.5 cm2. They stated that well-designed randomized trials are needed to address the limitation of the available literature and further the understanding of the optimal therapeutic options.

Combined Autologous Chondrocyte Implantation and Meniscus Reconstruction for Large Chondral Defect due to Discoid Lateral Meniscus Tear

Kato and colleagues (2018a) stated that discoid lateral meniscus tear leads to large chondral defect in the lateral compartment of the knee joint. There are few effective treatments for large chondral defect in both the tibial and femoral sides with severe degenerative lateral meniscus. These investigators developed a combined ACI and meniscus reconstruction technique using hamstring tendon. This technique allows biological reconstruction and avoids knee arthroplasty. In this single-case report (a 57-year old woman with 10 years of left knee joint pain and limited range of motion [ROM]), a novel technique was introduced as a pilot study. These investigators had only 3 cases and presented 1 case with second-look arthroscopic findings. While this case showed excellent short-term results, mid- or long-term results are still unclear. It is of concern that progression of OAs occurs with time; therefore, long-term follow-up is needed. The authors stated that this type of regenerative medicine is ever-expanding, however, the field is heavily influenced by practitioner acumen, surgical techniques, and development of operative procedures. They hope that this technique will contribute to the further development of ACI.

Combined Autologous Chondrocyte Implantation and Osteochondral Autograft Transfer for Large Knee Osteochondral Lesion

Kato and colleagues (2018b) noted that full-thickness knee cartilage defects greater than 4 cm2 are best treated with ACI. Since the articular cartilage surrounding the site of implantation does not always have the normal thickness desirable for successful engraftment, there may be benefit in combining ACI with OAT, which provides immediate restoration of condylar contour and mechanical function. These researchers presented the case of a 19 year-old man who sustained a traumatic anterolateral femoral condyle osteochondral fracture and underwent

arthroscopic knee surgery 3 months after injury to harvest healthy cartilage to be sent to the Japan Tissue Engineering Co., Ltd. (J-TEC) for cartilage culture. The patient was re-admitted after 4 weeks to undergo a procedure using the OATS and the J-TEC autologous cultured cartilage (JACC) system. Three 4.75-mm osteochondral cylindrical cores were harvested from non-weight-bearing areas of the knee and were transplanted to the lateral periphery of the lateral femoral condyle defect. The cultured cartilage was implanted to the remaining defect with a periosteal cover harvested from the anterolateral ridge of the lateral femoral condyle. Continuous passive ROM exercises and gait retraining were immediately initiated, with strict no weight-bearing precaution on the operated limb. Partial weight-bearing was allowed 4 weeks after surgery, which was progressed to full weight-bearing after another 2 weeks. The authors concluded that ACI must be viewed as a complementary procedure to osteochondral transplantation; and that although still without long-term follow-up to demonstrate results, this hybrid technique appeared to be a promising surgical approach and therapeutic option for large cartilage lesions, especially in the younger population.

Autologous Matrix-Induced Chondrogenesis

Autologouc matrix-induced chondrogenesis is a single-step surgery to repair deep chondral and subchondral lesions. During this surgery, the damaged cartilage is removed and the bone subjected to a marrow stimulation procedure (drilling or microfracture). A specially designed porcine collagen membrane is placed over the bone surface and is held in place with fibrin glue or is sutured around its periphery. This surgery is usually performed under general or spinal anesthesia. Autologous matrix-induced chondrogenesis may be performed arthroscopically or in an open surgery.

Aurich and co-workers (2017) stated that osteochondral lesions (OCL) of the ankle are a common cause of ankle pain. Although the precise pathophysiology has not been fully elucidated, it can be assumed that a variety of factors are responsible, mainly including traumatic events such as ankle sprains. Advances in arthroscopy and imaging techniques, in particular MRI, have improved the possibilities for the diagnosis of OCLs of the ankle. Moreover, these technologies aim at developing new classification systems and modern treatment strategies. These

investigators presented recommendations of the group "Clinical Tissue Regeneration" of the German Society of Orthopedics and Traumatology (DGOU) for the treatment of OCLs of the ankle. The review gave a concise overview on the results of clinical studies and discussed advantages and disadvantages of different treatment strategies. Non-operative treatment showed good results for selected indications in children and adolescents, especially in early stages of OCD. However, surgical treatment is usually indicated in OCLs in adolescents and adults, depending on the size and location of the lesion. Various arthroscopic and open procedures are frequently employed, including re-attachment of the fragment, local debridement of the lesion with fragment removal and curettage of the lesion, bone marrow-stimulation by microfracture or micro-drilling (antegrade or retrograde), and autologous matrix-induced chondrogenesis (AMIC) - with or without reconstruction of a subchondral bone defect or cyst by autologous cancellous bone grafting. Isolated subchondral cysts with an intact cartilage surface can be treated by retrograde drilling and possibly additional retrograde bone grafting. For larger defects or as salvage procedure, osteochondral cylinder transplantation (OATS or mosaicplasty) or MACT are recommended. Transplantation of so-called (osteochondral) mega grafts, such as autologous bone grafts or allografts, are used for very large osteochondral defects that cannot be reconstructed otherwise. Implantation of the so-called "small metal implants" -- such as HemiCAP Talus -- is reserved for selected cases after failed primary reconstruction. Corrective osteotomies are indicated in accompanying axial malalignments. The authors concluded that there are several different treatment strategies for OCLs, but clinical studies are rare and evidence is limited. Thus, interventional studies (e.g., randomized controlled trials (RCTs), but also observational studies, e.g., based on data of the Cartilage Registry of the German Society of Orthopedics and Traumatology (www.knorpelregister-dgou.de)) are needed.

Schiavone Panni and associates (2018) noted that AMIC is a treatment for focal full-thickness cartilage defects combining microfracturing with an exogenous I/III collagen matrix (Chondro-Gide). These researchers examined the 7 years outcomes of patients treated with the AMIC technique for knee chondral defects larger than 2 cm2. They hypothesized that the positive short-term outcomes achieved in the previous series would not deteriorate at a 7-year follow-up. A total of 21

patients treated with the AMIC technique were retrospectively analyzed. Patients were assessed through the IKDC subjective knee evaluation questionnaire and the Lysholm scoring system. All patients underwent a complete imaging study including radiographs and magnetic resonance. The median defect size was found to be 4.3 (range of 2.9 to 8) cm2. At a median follow-up of 7 (± 1.4) years, the mean IKDC score improved from 31.7 (± 8.9) points pre-operatively, to 80.6 (± 5.3) at the latest follow-up ($p < 0.05$). The mean Lysholm score improved from 38.8 (± 12.4) points pre-operatively to 72.6 (± 19.5) points at the last follow-up ($p < 0.05$). At the last follow-up, 76.2 % of patients were satisfied or extremely satisfied with their outcomes, while 66.6 % of patients showed good quality repair tissue on MRI. The authors concluded that AMIC was found to be an effective method to treat full-thickness knee chondral defects larger than 2 cm2, with significant clinical and functional improvement maintained over a 7-year follow-up. Level of Evidence = IV.

Bertho and co-workers (2018) noted that osteochondral defects due to advanced osteochondritis of the knee eventually cause osteoarthritis; AMIC may hold potential for overcoming the treatment challenges raised by defects larger than 2cm2. In a prospective, single-center, single-surgeon study, these researchers examined medium-term functional outcomes of AMIC; the secondary objective was to confirm the absence of adverse events (AEs). A total of 13 consecutive patients managed using AMIC between September 2011 and November 2016 were included. There were 8 males and 5 females with a mean age of 29 years (range of 15 to 51 years). Among them, 9 had had previous surgery. The ICRS grade was IV in 12 patients and III in 1 patient. The defects had a mean surface area of 3.7cm2 (range of 2.2 to 6.9 cm2) and mean depth of 0.5 mm (range of 0.4 to 0.8). In each patient, knee function was assessed by an independent examiner based on validated instruments (KOOS, subjective IKDC score, and VAS pain score). After a median follow-up of 24 months (range of 12 to 42 months; minimum of 1 year), 11 patients had significant improvements, with mean increases in the IKDC score and KOOS of 27 and 28 points, respectively. The scores remained stable after the 1st year. Of the 2 patients with poorer outcomes, 1 had a history of multiple surgical procedures and the other was a 51-year old woman with a defect surface area of 6.9 cm2. No post-operative complications were recorded. The authors concluded that AMIC was a reliable single-stage method that was both reproducible and

widely available; AMIC significantly improved knee function scores in patients with large osteochondral defects due to advanced osteochondritis of the knee. Moreover, these researchers stated that further studies are needed to confirm these preliminary findings. Level of Evidence = IV.

The authors stated that this study had several drawbacks. This trial was preliminary with only 13 patients. The minimum follow-up was only 12 months. The full measure of improvement appeared to be obtained within 1 year, with no change subsequently. There was no control group, but no published studies have compared AMIC to repair techniques other than microfractures.

Schagemann and associates (2018) presented the first retrospective study that compared 2 various AMIC surgical interventions to repair grade III to IV cartilage defects in the knee. Patients who underwent minimally invasive (arthroscopy) or open (mini-arthrotomy) AMIC were followed-up to 2 years to examine if minimally invasive AMIC was superior to open procedures. A total of 50 patients with focal and contained grade III to IV articular cartilage defects in the knee joint were followed in a consecutive cohort study; 20 patients were treated arthroscopically (female 7, male 13; age: mean 38.2 years, range of 18 to 70 years; BMI: mean of 27.0, range of 18.7 to 34.7; defect size: mean of 3.1 cm2, range of 1.0 to 6.0 cm2), and 30 patients via mini-arthrotomy (female 13, male 17; age: mean of 34.4 years, range of 14 to 53 years, BMI: mean of 23.9, range of 18.4 to 28.7; defect size: mean of 3.4 cm2, range of 1.5 to 12.0 cm2). The primary defect localization was the medial femoral condyle. AMIC resulted in a significant improvement of VAS pain, KOOS and Lysholm scoring for up to 2 years compared to pre-op. Outcome analysis revealed no significant differences between the 2 different surgical approaches. The authors concluded that the findings of this study suggested that mini-open AMIC was equivalent to the arthroscopic procedure. The anticipatory hypothesis that minimally invasive approaches bring greater patient benefit per se could not be confirmed. Thus, these investigators recommended to perform AMIC where indicated and suggested that the surgeon's personal skills profile guide the choice of surgical approach. Level of Evidence = III.

In a retrospective study, de Girolamo et al (2018) examined the clinical follow-up (8 years) and failure rate (revision rate/conversion to arthroplasty) of patients with hip chondral lesions associated with femoro-acetabular impingement (FAI) and compared over time the treatment by microfracture (MFx) and AMIC. Patients aged between 18 and 55 years, with acetabular grade III and IV chondral lesions (Outerbridge), measuring 2 to 8 cm2 operated on at least 8 years before enrollment. Exclusion criteria were rheumatoid arthritis, dysplasia, or axial deviation of the femoral head. There were no arthritic lesions, Tonnis of less than 2, or joint space of at least 2 mm. MFx was performed with an awl, and the Chondro-Gide membrane used for the AMIC procedure was placed without glue. Outcomes used modified Harris hip score (mHHS) at 6 months and yearly for 8 years and patient acceptable symptomatic state. Among 130 patients, 109 fulfilled inclusion criteria; 50 were treated by MFx and 59 by AMIC. The mHHS significantly improved in both groups from 46 ± 6.0 to 78 ± 8.8 for mHHS at 6-12 months, even for lesions greater than 4 cm2. From 2 to 8 years, mHHS in the AMIC group was better than in the MFx group ($p < 0.005$). This mHHS improvement in the AMIC group was maintained through the 8-year follow-up period, whereas it deteriorated after 1 year in the MFx group ($p < 0.005$); 11 patients (22 %) in the MFx group required total hip arthroplasty (THA); none in the AMIC group did. Patient acceptable symptomatic state analysis confirmed similar short-term improvement, but a significant ($p < 0.007$) degradation after 2 to 8 years in MFx patients. The authors concluded that MFx and AMIC techniques led to marked clinical short-term improvement in patients with chondral defects resulting from FAI in the first 2 years. However, AMIC gave significantly better results as measured by mHHS, which were maintained after 8 years, the results of MFx in the hip deteriorated over time with 22 % of patients undergoing conversion to THA. No patient in the AMIC group was converted to THA; the results of AMIC appeared stable over time and independent of lesion size. Level of Evidence = III.

Usuelli et al (2018) examined clinical and radiological outcomes of patients treated with a new all-arthroscopic AMIC (AT-AMIC) technique with autologous bone graft for talar osteochondral defects at a follow-up of 24 months. A total of 20 patients underwent the AT-AMIC procedure and autologous bone graft for type III and IV talar osteochondral lesions . Patients were evaluated pre-operatively and at 6, 12, and 24 months

post-operatively using the AOFAS score, the VAS, and the SF-12. Radiological assessment included CT, MRI, and magnetic resonance observation of cartilage repair tissue (MOCART). All scores significantly improved ($p < 0.05$) with respect to pre-operative values after 6 months. Further improvements were detected at 24 months (AOFAS, from 57.1 ± 14.9 before surgery to 86.6 ± 10.9 after 24 months; VAS, from 8.1 ± 1.4 to 2.5 ± 2.2; SF-12, from 29.9 ± 4.1 to 48.5 ± 6.9 and from 43.8 ± 2.9 to 53.1 ± 3.9, respectively, for Physical and Mental component score). Lesion area significantly reduced from 111.1 ± 43.2 mm2 pre-operatively to 76.9 ± 38.1 mm2 ($p < 0.05$) at final follow-up as assessed by CT, and from 154.1 ± 93.6 to 94.3 ± 61.3 mm2 ($p < 0.05$) as assessed by MRI. The mean MOCART score was 42.8 ± 23.5 points and 50.9 ± 24.9 points, respectively, at 12 and 24 months after surgery ($p < 0.05$). The authors concluded that AT-AMIC with autologous bone grafting has proven to be a safe and effective minimal invasive technique, able to rapidly and significantly improve pain, function, and radiological healing of osteochondral talar lesions, with progressive further improvements up to 24 months. These researchers stated that orthopedic surgeons specialized in foot and ankle surgery should adopt the AT-AMIC technique for the treatment of osteochondral talar lesions, which proved to be effective and minimally invasive, avoiding malleolar osteotomy with a low risk of complications. Level of Evidence = IV.

The authors stated that the drawbacks of this study included the relatively small number of patients (n = 20) that did not allow for sub-population analysis, and the lack of a control group, in particular with AMIC open procedure. Another drawback was represented by the lack of a delayed gadolinium-enhanced MRI (dGEMRIC) assessment of the repair tissue, which could have given useful information regarding tissue quality. However, the combination of MRI and CT information provided a good evaluation of the neo-cartilage and subchondral bone after the AT-AMIC surgical procedure. Another important drawback was the lack of sport activity assessment, especially in young patients. These researchers stated that further studies will focus on the evaluation of the return to the sport in patients treated with AT-AMIC technique and autologous bone graft, also considering the type of sports activity (high or low impact) and time taken to return to sports.

Astur et al (2018) examined the clinical and functional results of patients diagnosed with full-thickness chondral defects on symptomatic knees who underwent a biological repair technique using AMIC (n = 7). The Lysholm, Kujala and VAS of pain questionnaires were applied before and 12 months after the surgery. Nuclear MRI were evaluated 12 months after surgery according to MOCART cartilage repair tissue score. Of the 7 patients evaluated, 3 presented defects classified as grade III and 4 as grade IV according to the ICRS classification. Chondral defects were located in the medial femoral condyle (n = 2), patella (n = 2), and trochlea (n = 3). The mean age of the patients (6 men and 1 woman) was 37.2 years (24 to 54 years). The mean chondral defect size was 2.11 cm2 (1.0 to 4.6 cm2). After 12 months, post-operative nuclear mMRI showed re-surfacing of the lesion site with scar tissue less thick than normal cartilage in all patients. The mean MOCART score was 66.42 points. A significant decrease in pain and an improvement in the Lysholm and Kujala scores were observed. The authors concluded that the use of the collagen I/III porcine membrane was favorable for the treatment of chondral and osteochondral lesions of the knee when assessing the results using the VAS, Lysholm, and Kujala scores 1 year after surgery, as well as when assessing the MRI of the lesion 6 months after surgery. The main drawbacks of this study were its small sample size (n = 7) , short-term follow-up (12 months), and chondral defects from different regions of the knee.

Baumfeld et al (2018) reported early post-operative clinical results of patients submitted to the AT-AMIC technique and autologous bone graft, when necessary, for OLT's at an 8-month minimum follow-up. This was a case series of 17 consecutive patients that were submitted to AT-AMIC, between January of 2016 and April of 2017. A total of 9 men and 8women, between 15 and 67 years were diagnosed with OLTs with the typical history of deep ankle pain and corresponding MRI injury. Surgery was proposed only after failure of conservative treatment of at least 3 months. Patients answered the AOFAS score pre-operatively and at the last follow-up, ranging from 8 to 20 months. Average size of OLTs were 1.16 cm2, with Raikin 4 location being the most common (71 %). Calcaneal osteotomy was the most common associated procedure, with 18 %. Average follow-up was 10.8 months. Average AOFAS before surgery was 46.4, increasing to 89.5 at the last follow-up. This difference was statistically significant with a p-value of < 0.001. No complications

were observed and no changes in the post-operative protocol were needed. The authors concluded that AT-AMIC was a reliable and reproducible method of treatment for OLTs, reaching high clinical post-operative scores, with a very low rate of complications. Moreover, these researchers stated that further comparative study is needed to prove its efficacy.

Galla et al (2019) examined complication rates and post-operative outcomes in patients with osteochondral lesions of the talus who underwent an AMIC procedure with autologous spongiosa grafting without malleolar osteotomy. A total of 23 patients with a mean age of 35.6 ± 13.9 years were included in this study. The mean follow-up was 33.5 ± 10.4 months (range of 24 to 52.9 months). The clinical outcomes were evaluated using the VAS and the Foot Function Index (FFI). Post-operatively, lesion healing was assessed using the MOCART protocol. There were no intra-operative or peri-operative complications. In 1 patient, arthroscopic arthrolysis was performed due to painful arthrofibrosis. The mean VAS significantly decreased from 7.6 ± 1.1 (range of 4.2 to 9.3) to 1.4 ± 2.2 (range of 0 to 7.4) ($p < 0.001$). The mean FFI significantly improved from 46.8 ± 14.3 (range of 24.3 to 80.8) to 15.9 ± 11.4 (range of 10.0 to 51.7) ($p < 0.001$). The mean MOCART score at 1-year follow-up was 74.1 ± 12.4 (range of 50 to 95). Both pre-operative and post-operative pains were significantly higher for smokers when compared to non-smokers. The authors concluded that the findings of this study indicated that AMIC procedure could be performed through the antero-lateral and antero-medial arthrotomy without malleolar osteotomy. Therefore, the possible complications associated with malleolar osteotomy can be avoided. These researchers stated that the AMIC procedure without a malleolar osteotomy can be considered a safe and reliable procedure in patients with osteochondral lesions localized anterior to the mid-line in the sagittal plane. Level of Evidence = IV.

In a prospective RCT, Fossum et al (2019) examined any difference in the outcome of AMIC as compared with collagen-covered autologous chondrocyte implantation (ACI-C) for the treatment of greater than or equal to 1 chondral or osteochondral defects of the distal femur and/or patella. The inclusion period was set to 3 years, and the aim was to include 80 patients (40 in each group). Patient inclusion was broad, with few exclusion criteria. The primary outcome was change in KOOS at 2

years as compared with baseline. The secondary outcomes were the number of failures in each group at 2 years and the change in KOOS subscale, Lysholm, and pain VAS scores at 2 years as compared with baseline. A 2-sample t test with a significance level of $p < 0.05$ was used to compare the change in score from baseline between groups. A total of 41 patients over 3 years were included in the study: 21 in the ACI-C group and 20 in the AMIC group. All the patients had prior surgery to the index knee. At 2-year follow-up, the clinical scores for both groups improved significantly from baseline. No significant differences between groups were observed in the change from baseline for KOOS (AMIC, 18.1; ACI-C, 10.3), any of the KOOS subscales, the Lysholm score (AMIC, 19.7; ACI-C, 17.0), or the VAS pain score (AMIC, 30.6; ACI-C, 19.6); 2 patients in the AMIC group had progressed to a total knee replacement by the 2-year follow-up as compared with 0 in the ACI-C group. The authors concluded that at 2-year follow-up, no significant differences were found regarding outcomes between ACI-C and AMIC. These researchers stated that mid- and long-term results will be important; further basic and clinical research is needed in this field, as all available surgical methods today are imperfect for cartilage repair. Level of Evidence = II.

The authors stated that the main drawback of this study was the small number of patients in each group. After 3 years, these investigators had included 41 patients. They estimated that at least 3 more years would be needed to reach the 80 patients called for by the power calculation, and they decided to end the inclusion of patients for economic and practical reasons. Another drawback was the broad inclusion criteria used, which resulted in heterogeneity regarding the location of defects, number of defects, etiology of the defects, duration of symptoms, and age for the group as a whole. A difference in sex distribution was observed, with a higher percentage of women in the AMIC group. If female patients have a poorer outcome than male patients, this would have affected our results for the AMIC group. However, other trials, including the authors' own, have not shown the same correlation. Four patients in the ACI-C group were, at the time of final surgery, shown to have a total defect size smaller than the size described in the inclusion criteria. This was due to over-estimation of the non-debrided defect size during arthroscopy. These patients were not excluded from the study, and their results could have inflated the outcome of the ACI-C group. Many patients had signs

of early osteoarthritis, even at baseline, but no patients were included who were clear candidates for unicompartmental / total knee replacement or osteotomy. Unloading braces were not used for lesions in the femoro-tibial articulation, but any negative effect that this practice could have on the outcome scores would be applicable to both groups. The broad inclusion of patients might have led to the inclusion of patients with some degree of a chronic pain condition. No acute lesions were included in the trial, and this could have had a negative impact on the outcome scores in both groups. Previous microfracture is known to negatively affect the outcome of subsequent cartilage regeneration procedures. Although these researchers saw the same tendency in this trial, the disadvantage was equally distributed between the groups. Since the objective of this study was to compare the results of AMIC versus ACI-C and not to evaluate the effectiveness of the treatments, these researchers did not consider the broad inclusion criteria a major drawback of the trial's conclusion. The heterogeneity of the population and the chronicity of the defects made it more relevant to extrapolate the results of this trial to the typical group of patients observed in a clinical setting.

Gudas et al (2019) examined the post-operative clinical outcome of AMIC for characterized cartilage lesions. A total of 15 patients with articular cartilage (AC) defects of the knee were included in the study; AC defects were characterized intra-operatively by ICRS score. Grade III to IV AC lesions were treated with AMIC; grade I to II lesions were left untreated. Patients were divided into subgroups and clinically evaluated by subjective IKDC and Tegner scores at median follow-up of 4.5 years. A total of 28 AC defects were diagnosed (1.9/patient). Multiple subgroup had larger diagnosed (7 ± 2.3 cm2, p = 0.022) and untreated (3.1 ± 2.3 cm2, p = 0.012) lesion areas than the single subgroup. Partly treated subgroup had larger untreated defect areas (3.6 ± 2.3 cm2, p = 0.025) than the treated subgroup. Average subjective IKDC values of total group and individual subgroups improved significantly at follow-up. More patients restored their previous activity levels (p = 0.026) and had higher incremental subjective IKDC scores (p = 0.014) in the single subgroup than the multiple subgroup. Diagnosed defect size negatively correlated to subjective IKDC incremental (r = -0.624, p = 0.023) and post-operative scores (r = -0.545, p = 0.054) in total group. The authors concluded that AMIC could have a clinically relevant outcome for patients with single or multiple knee AC lesions; however, clinical outcome was superior in

patients with a single defect per knee. Patients with single defects returned to previous physical activity levels significantly faster than patients with multiple defects. Diagnosed AC defect areas negatively correlated to clinical improvement at follow-up. These researchers stated that more effective diagnostics of early cartilage degeneration might improve expected clinical outcome following the treatment.

The authors stated that drawbacks of the study included a small number of patients (n = 15). It did not reveal more significant changes among different treatment groups. These researchers did not use more clinical outcome scores for in-depth analysis of what specific knee motions were limited due to the cartilage defect. An important drawback of this trial was the lack of interim results that would enable the analysis of longer follow-up. Another drawback was the lack of re-imaging, histological sampling of the fibrous repair cartilage. Lack of the repair tissue integration, as a result of micro-motion, macro-motion, and subsequently loosening, might have impaired clinical outcome.

Gao and colleagues (2019) noted that the addition of a type I/III collagen membrane in cartilage defects treated with microfracture has been advocated for cartilage repair, termed AMIC". In a systematic review, these researchers examined the current clinical evidence regarding AMIC for focal chondral defects. They conducted a systematic review by searching PubMed, ScienceDirect, and Cochrane Library databases. Inclusion criteria were clinical studies of AMIC for articular cartilage repair, written in English. Relative data were extracted and critically analyzed. PRISMA guidelines were applied, the methodological quality of the included studies was assessed by the modified Coleman Methodology Score (CMS), and aggregate data were generated. A total of 28 clinical articles were included: 12 studies (245 patients) of knee cartilage defects, 12 studies (214 patients) of ankle cartilage defects, and 4 studies (308 patients) of hip cartilage defects. The CMS demonstrated a sub-optimal study design in the majority of published studies (knee, 57.8; ankle, 55.3; hip, 57.7). For the knee, 1 study reported significant clinical improvements for AMIC compared with microfracture for medium-sized cartilage defects (mean defect size of 3.6 cm2) after 5 years (Level of Evidence = I). No study compared AMIC with MACI in the knee. For the ankle, no clinical trial was available comparing AMIC versus microfracture or MACI. In the hip, only 1 analysis (Level of Evidence = III) compared

AMIC with microfracture for acetabular lesions. For medium-sized acetabular defects, 1 study (Level of Evidence = III) found no significant differences between AMIC and MACI at 5 years. Specific aspects not appropriately discussed in the currently available literature included patient-related factors, membrane fixation, and defect properties. No treatment-related adverse events (AEs) were reported. The authors concluded that the findings of this systematic review revealed a paucity of high-quality, randomized controlled trials (RCTs) testing the AMIC technique versus established procedures such as microfracture or MACI. Evidence is insufficient to recommend joint-specific indications for AMIC. These researchers stated that additional non-biased, high-powered, RCTs will provide better clinical and structural long-term evidence, thereby helping to define possible indications for this technique.

Becher and associates (2019) stated that microfracture is an established method to treat osteochondral defects of the talus. The value of the addition of an acellular matrix is still under debate. These researchers compared the results of arthroscopic microfracture versus arthroscopic AMIC using a collagen I/III matrix in the management of articular cartilage defects of the talus. Patients with a minimum follow-up of 5 years after arthroscopic management for an articular cartilage defect of the talus with either microfracture alone or an additional acellular matrix were matched according to age, sex and BMI. The Hannover Scoring System for the ankle (HSS) and a VAS for pain, function and satisfaction were used to evaluate the clinical outcome. Post-operative MRI was used to assess cartilage repair tissue based on the degree of defect repair and filling of the defect, integration to border zone, surface of the repair tissue, structure of the repair tissue, and subchondral bone alterations. A total of 32 patients (16 microfracture, 16 AMIC) were included. No significant between-group differences were observed in demographic data and pre-operative score values. Both groups showed statistically significant improvement when comparing the pre- and post-operative score values. No statistically significant differences were identified between the median values of the groups with the HSS (microfracture: 82 (range of 71 to 96) points; AMIC 88 (range of 40 to 98) points). Accordingly, no significant differences were observed for the VAS pain (microfracture: 0.95 (range of 0 to 3.8); AMIC: 1.0 (range of 0 to 8.5)), VAS function (microfracture: 8.4 (range of 3.5 to 10); AMIC: 9.0 (range of 1.5 to 10)) and VAS satisfaction (microfracture: 8.9 (range of 2.8 to 10); AMIC: 9.45 (range of 1.5 to 10));

MRI showed regeneration of tissue in the treated area without differences between the 2 groups. The authors concluded that good clinical results were observed for arthroscopic microfracture with or without an additional acellular collagen I/III matrix in the treatment for articular cartilage defects of the talus. It appeared that for defects as treated in this study, it was not worthwhile adding the collagen I/III matrix to the microfractures. Level of Evidence = III.

Andrade and co-workers (2021) systematically analyzed the post-operative clinical, functional, and imaging outcomes, complications, re-operations, and failures following patella-femoral cartilage restoration surgery. This review was conducted according to the guidelines of PRISMA. PubMed, Embase, and Cochrane Library databases were searched up to August 31, 2018, to identify clinical studies that examined surgical outcomes of patella-femoral cartilage restoration surgery. The Methodological Index for Non-Randomized Studies (MINORS) was used to assess study quality. A total of 42 studies were included comprising 1,311 knees (mean age of 33.7 years and 56 % males) and 1,309 patello-femoral defects (891 patella, 254 trochlear, 95 bipolar, and 69 multiple defects, including the patella or trochlea) at a mean follow-up of 59.2 months. Restoration techniques included ACI (56 %), particulated juvenile allograft cartilage (12 %), AMIC (9 %), osteochondral autologous transplantation (9 %), and osteochondral allograft transplantation (7 %). Significant improvement in at least 1 score was present in almost all studies and these surpassed the minimal clinically important difference threshold. There was a weighted 19 %, 35 %, and 6% rate of reported complications, re-operations, and failures, respectively. Concomitant patella-femoral surgery (51 % of patients) mostly did not lead to statistically different post-operative outcomes. The authors concluded that numerous patella-femoral restoration techniques resulted in significant functional improvement with a low rate of failure. No definitive conclusions could be made to determine the best surgical technique since comparative studies on this topic are rare, and treatment choice should be made according to specific patient and defect characteristics. Level of Evidence = IV.

Furthermore, an UpToDate review on “Overview of surgical therapy of knee and hip osteoarthritis” (Mandl and Martin, 2020) does not mention autologous matrix-induced chondrogenesis as a therapeutic option.

Comparison of Autologous Chondrocyte Implantation and Osteochondral Allograft Transplantation of the Knee

Sochacki and colleagues (2021) compared the re-operation rates, risk factors for re-operation, 30-day complication rates, as well as cost differences between ACI and osteochondral allograft transplantation (OCA) of the knee in a large insurance database. Subjects who underwent knee ACI or OCA with minimum 2-year follow-up were queried from a national insurance database. Re-operation was defined by ipsilateral knee procedure after index surgery. Multivariate logistic regression models were built to determine the effect of independent variables (age, sex, tobacco use, obesity, diabetes, and concomitant osteotomy) on re-operation rates. The 30-day complication rates were examined using ICD-9-CM codes; and the cost of the procedures per patient was calculated. Statistical comparisons were made; all "p" values were reported with significance set at $p < 0.05$. A total of 909 subjects (315 ACI and 594 OCA) were included (mean follow-up of 39.2 months). There was a significantly higher re-operation rate after index ACI compared with OCA (67.6 % versus 40.4 %, $p < 0.0001$). Concomitant osteotomy at the time of index procedure significantly reduced the risk for re-operation in both groups (odds ratio [OR] 0.2, $p < 0.0001$ and OR 0.2, $p = 0.009$). The complication rates were similar between ACI (1.6 %) and OCA (1.2 %) groups ($p = 0.24$). Day of surgery payments were significantly higher after ACI compared with OCA ($p = 0.013$). The authors concluded that ACI had significantly higher re-operation rates and cost with similar complication rates compared with OCA. Concomitant osteotomy significantly reduced the risk for re-operation in both groups.

Two-Stage Bone and Meniscus Allograft and Autologous Chondrocytes Implant for Unicompartmental Osteoarthritis

Alvarez-Lozano and colleagues (2022) analyzed the clinical and radiographic evolution of patients with knee unicompartmental OA and axis alteration and osteochondral lesions in the femoral condyle, treated with tibial plateau and meniscus allograft and cultured autologous chondrocyte implantation in the femur in two steps. A total of 16 patients, average age of 56 years, were included in a cohort study. These investigators carried out an osteotomy with tibia plateau allograft, including the meniscus. In a second surgery, the chondrocyte fibrin

scaffold was placed in the femur. Clinical symptoms and function were measured using KSSR and KOOS scores. Wilcoxon's test was carried out to compare the results over the 2-year follow-up period. Mean KSSR before surgery was 35.69 (SD: 3.75) points, rising to 67 (SD: 15.42) at 3 months, 95.88 at 12 months (SD: 2.68) and 96.31 at 24 months (SD: 2.24). The KOOS before surgery was 65.14 (SD: 16.34), rising to 72.68 after 3 months (SD: 19.15), 76.68 at 12 months (SD: 18.92) and 64.28 at 24 months (SD: 11.79); 4 of 5 patients returned to engaging in the activity that they had stopped practicing; 3 patients experienced collapse of the tibia allograft, and they later needed a prosthesis. The authors concluded that simultaneous tibia plateau allograft and autologous chondrocyte implantation in the femur, after correction of the angular deformity, were performed, restoring the anatomy of the medial compartment and knee function in 82 % of the patients 2 years after the operation. Level of evidence = IV. This was a small (n = 16) study that provided mid-term results of 2-stage bone and meniscus allograft and ACI for knee unicompartmental OA. These findings need to be validated by well-designed studies.

Autologous Matrix-Induced Chondrogenesis (AMIC) for Chondral Defects of the Knee

Migliorini et al (2022) noted that chondral defects of the knee are common; and their treatment is challenging. Both autologous matrix-induced chondrogenesis (AMIC) and membrane-induced autologous chondrocyte implantation (MACI) have been used to manage chondral defects of the knee. It is debated whether AMIC and MACI provide equivalent outcomes for the management of chondral defects in the knee at mid-term follow-up. Despite the large number of clinical studies, the optimal treatment is still controversial. These researchers examined if AMIC would provide superior outcomes than MACI at mid-term follow-up. Data sources included PubMed, Google scholar, Embase and Scopus databases. A total of 503 studies were initially obtained and 107 were excluded as they were duplicates. A further 349 articles were excluded because they did not match the inclusion criteria: not focused on MACI or AMIC (n = 225), not focusing on knee (n = 37), study design (n = 51), not reporting quantitative data under the outcomes of interest (n = 12), combined with other committed cells (n = 12), other (n = 8), language limitations (n = 3), not clearly stating the duration of the follow-up (n = 1);

therefore, a total of 47 articles were available for this study. The AMIC group reported greater values of IKDC (mean difference [MD] 7.7; p = 0.03) and Lysholm (MD 16.1; p = 0.02) scores. Similarity was found concerning the VAS (p = 0.5) and Tegner (p = 0.2) scores. The AMIC group showed lower rate of failures (OR 0.2; p = 0.04). Similarity was found concerning the rate of hypertrophy (p = 0.05), knee arthroplasty (p = 0.4) and revision surgery (p = 0.07). The authors concluded that AMIC may provide better outcomes than MACI for chondral defects of the knee. Moreover, these researchers stated that further studies are needed to verify these findings in a clinical setting.

These investigators pointed out that all statistical analyses were carried out regardless of the surgical approach. Indeed, authors performed the procedures using arthrotomy, mini-arthrotomy or arthroscopy. The MACI cohort included a larger number of studies and related procedures compared with the AMIC group. This discrepancy may generate biased results and influence the rate of uncommon complications related to poorer outcome. Given the lack of quantitative data, the average return to daily activities and/or sport participation were not examined. All the membranes considered in the present investigation were cell-free and bioresorbable (collagenic or hyaluronic): this study did not consider cell-based or more innovative synthetic scaffolds. Moreover, the typology of membrane fixation (fibrin glue, suture, both methods, or no fixation) was not considered as separate. Given the lack of relevant data, it was not possible to overcome these limitations. Many investigators did not differentiate between primary and revision settings, and several studies included patients who received combined surgical procedures. Two studies performed membrane-assisted ACT (MACT). In MACT, chondrocytes were harvested, cultivated and expanded into a membrane in the same fashion of MACI. The chondrocyte-loaded membrane was then carefully implanted into the defect using custom-made instruments in a full-arthroscopic fashion. Given these similarities, these researchers analyzed MACT and MACI as a single entity. The lack of detailed information did not allow these researchers to analyze the etiology of chondral defects as separate data sets. They stated that these limitations suggested cautious interpretation of the conclusions of this study.

Autologous Chondrocyte Implantation for Young Patients

Carey et al (2021) noted that MACI (autologous cultured chondrocytes on porcine collagen membrane) was granted FDA approval in 2016 for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults. The approval was supported by the pivotal 2-year SUMMIT (Superiority of MACI Implant Versus Microfracture Treatment) study, which was a prospective, randomized, open-label, parallel group, multi-center, phase-III clinical trial carried out in 144 adult patients (72 MACI and 72 microfracture). The study demonstrated superior effectiveness of MACI compared with arthroscopic microfracture in the treatment of patients, age of 18 to 54 years, with at least 1 symptomatic Outerbridge Grade III or IV focal cartilage defect of the knee. In accordance with the Pediatric Research Equity Act, Vericel and FDA agreed upon an initial pediatric study plan to conduct a study in patients aged 10 to 17 years; the plan was submitted with the MACI Biologics License Application. The ongoing post-marketing study, which was required as a condition of FDA approval, "PEdiatric Autologous cultured chondrocytes treatment of cartilage defects in the Knee" (PEAK Trial) is a prospective, randomized, open-label, parallel group, 2-year, multi-center clinical trial being carried out at 10 sites in the U.S. A total of 45 patients, age of 10 to 17 years, will be randomized to receive a 1-time treatment with MACI or microfracture (2:1, 30 MACI:15 microfracture). The primary efficacy endpoint is the percentage of patients who respond to study treatment after 2 years, defined as patients who have greater than or equal to 10-point improvement on both the pain and function (sports and recreational activities) subscales of the KOOS-Child from baseline to Year 2. The PEAK Trial is the only ongoing RCT studying chondral and osteochondral defect therapeutic options in children and adolescents to-date that incorporates the FDA's feedback on post-marketing study requirements for the treatment of cartilage defects in pediatric patients.

These researchers stated that because the incidence of symptomatic cartilage lesions in the 10 to 17 years pediatric age group requiring surgical restoration is quite rare, significant challenges are anticipated to enroll an adequate number of pediatric patients. Therefore, the clinical study is limited in scope (45 patients planned to be treated and no hypothesis-testing) with a 4.5-year enrollment period. Limitations of the

PEAK Trial include the relatively small sample size that limits the power to perform statistical testing between treatment groups. The validity of the results of this study is not negated by the small sample size given the rigorous study design and conduct, multiple secondary endpoint assessments to support the primary efficacy analysis, and the availability of adult data for extrapolation. Additional limitations of the study design include lack of stratification for osteochondritis dissecans (OCD) versus chondral defects because of the limited sample size. However, in an attempt to minimize confounders, the study will limit defect location to the femur and exclude subjects requiring concomitant ligament repair. The sponsor and FDA aimed to design a study that could be completed in the proposed timeframe, thereby limiting the sample size.

In a systematic review, Migliorini et al (2023) examined the safety and effectiveness of ACI for chondral defects of the knee in skeletally immature patients. Current available data from patients reported outcome measures (PROMs) and complications were collected, analyzed, and discussed. This systematic review was carried out according to the PRISMA guidelines. The following databases were accessed in May 2022: PubMed, Google scholar, Embase, and Scopus. All the clinical studies examining the effectiveness of ACI for the management of chondral defects of the knee in skeletally immature patients were accessed. Studies on the treatment of patients with surgical procedures other than ACI were ineligible, nor were studies with a follow-up duration of shorter than 12 months. Results from 9 studies (251 procedures) were collected; 32 % (80 of 251) of patients were females. The mean length of follow-up was 44.2 ± 29.4 (range of 12 to 115) months. The mean age of the patients was 16.4 ± 0.7 (range of 15 to 17) years. The KOOS and IKDC increased + 41.9/100 (p = 0.003) and + 33.2/100 (p = < 0.0001) points, respectively. The Lysholm Knee Score improved + 20.6/100 (p = 0.02) points. The VAS for pain was lowered -- 3.6/10 (p = 0.004) points. The Tegner scale did not show any statistically significant improvement from baseline to follow-up (p = non-significant). The rate of graft hypertrophy was 12.5 % (5 of 40 patients), and the rate of failure 5.6 % (8 of 142 patients). The authors concluded that ACI for chondral defects of the knee was effective to improve PROMs in skeletally immature patients; however, the safety profile of ACI still remains controversial. Level of Evidence = III.

Microfracture- and Xeno-Matrix-Induced Chondrogenesis for the Treatment of Focal Traumatic Cartilage Defects of the Knee

In a retrospective study, Allegra et al (2023) examined clinical and instrumental outcomes of the autologous matrix-induced chondrogenesis (AMIC) technique for the treatment of isolated traumatic condyle and femoro-patellar cartilage lesions. A total of 25 patients (12 men, 13 women, mean age of 47.3 years) treated between 2018 and 2021 were reviewed and sub-divided into 2 groups based on age (Group A, age of less than 45 years; Group B, age of greater than 45 years). A clinical evaluation was carried out using the IKDC score, Lysholm score and VAS. Cartilage regeneration was evaluated via MRI (1.5 Tesla) and classified according to a MOCART scoring system. At a minimum follow-up of 2 years, Group A patients obtained greater instrumental results in comparison to group B: in fact, the MOCART score was statistically significantly correlated with the IKDC score ($r = 0.223$) ($p < 0.001$) exclusively in group A. The authors concluded that the AMIC technique demonstrated satisfying mid-term clinical results in all patients, regardless of age. According to MOCART score, the procedure appeared to be more beneficial for patients under the age of 45 years in term of regenerating tissue; however, a low MOCART value does not equate to a higher rate of failure or revision surgery. These researchers stated that further randomized studies are needed to examine if the procedure is safe and would reduce the risk of post-traumatic osteoarthritis in patients over 45 years of age.

The authors stated that this study had 2 main drawbacks. First, the limited number of patients enrolled (n = 25), which, however, was in line with the other reports cited, given the rarity of the lesions treated with this technique. Second, the non-uniform anatomic distribution of injuries. Compared to an medial femoral condyle (MFC) lesion, a trochlear lesion receives a different load. de Windt et al (2009) revealed some factors related to a better clinical outcome in patients treated using 1st-generation ACI or MACT or microfracture: defects located at the MFC and patients younger than 30 years, especially those with acute lesions.

Autologous Chondrocyte Transplantation for the Treatment of Osteoarthritis

Fares et al (2024) noted that tissue engineering and cartilage transplantation constitute an evolving field in the treatment of osteoarthritis, with therapeutic and clinical promise shown in ACT. In a systematic review, these investigators examined current clinical trials that employed ACT and evaluated its effectiveness in the treatment of osteoarthritis. PubMed, Ovid Medline, and Google-Scholar were searched up until February 2023. Inclusion criteria consisted of clinical trials that entailed autologous cartilage transplantation for the treatment of osteoarthritis. Clinical, imaging, arthroscopic, as well as histologic outcomes were evaluated. A total of 15 clinical trials, entailing 851 subjects, were included in this review. All studies used ACT in the treatment of knee osteoarthritis via various scaffolds: collagen-based (10 studies), polymer-based (2 studies), hyaluronic-acid based (2 studies), and spheroid technology (1 study). Clinical improvement of patients undergoing ACT was noted in 14 studies; 5 demonstrated superior clinical outcomes compared to the control group, while 1 showed inferiority compared to mesenchymal stem cells (MSCs). Post-operative imaging was employed to examine the degree of cartilage regeneration in 11 studies; 10 showed signs of cartilage recovery with ACT, 4 showed no difference, and 2 showed worse outcomes when compared to controls. Second-look-arthroscopy was carried out in 3 studies, which reported varying degrees of improvement in cartilage regeneration. Histologic analysis was conducted in 4 studies and generally revealed promising results. The authors concluded that while improved clinical outcomes were reported, conflicting findings in post-operative outcome analysis raised questions regarding the unequivocal utility of ACT. These researchers stated that further investigations with control groups, randomization, and appropriate blinding are needed.

Autologous Platelet-Rich Plasma and Fibrin-Augmented Minced Cartilage Implantation for the Treatment of Chondral Lesions of the Knee

Blanke et al (2024) stated that the treatment of cartilage lesions remains a challenge; MACI has evolved to become the gold standard procedure. However, this 2-step procedure has crucial disadvantages, and the 1-step minced cartilage procedure has gained attention. In a retrospective

study, these researchers examined the clinical and radiological outcome of an all-autologous minced cartilage technique in the treatment of cartilage lesions of the knee. This trial included 71 patients (38.6 years ± 12.0, 39.4 % women) with a MRI-confirmed grade III to V cartilage defect at the medial femur condyle (n = 20), lateral femur condyle (n = 2), lateral tibia plateau (n = 1), retro-patellar (n = 28) and at the trochlea (n = 20) were included. All subjects were treated with an all-autologous minced cartilage procedure (AutoCart). Clinical knee function was assessed by the Tegner score, VAS, the subjective and objective evaluation form of the IKDC and the KOOS. MRI analyses were carried out by MOCART 2.0 knee score. Follow-up examination was 13.7 ± 4.2 (12 to 24) months post-operative. All clinical scores significantly improved following surgical intervention ($p < 0.0001$), especially the subgroup sports and recreation of KOOS showed clear changes from baseline in the follow-up examination. In the post-operative MRI evaluation, 39 of 71 patients showed a complete fill of the cartilage defect without subchondral changes in 78 % of the patients in the MOCART 2.0 score in the follow-up analysis. None of the subjects showed adverse effects, which were linked to the minced cartilage procedure during the time of follow-up. The authors concluded that an all-autologous minced cartilage technique for chondral lesions at the knee joint appeared to be a safe and effective treatment with good clinical and radiological short-term results. Level of Evidence = IV.

The authors stated that this study had several drawbacks. First, there was no matched control group, which made it difficult to firmly examine the superior clinical effectiveness of the technique. Second, MRIs were carried out at different follow-ups and with different protocols. Moreover, the short-term follow-up restricted the ability to draw any conclusions on the superiority of other chondrocyte transplant procedures in the long-term outcome. Third, all procedures were conducted in a mini-open approach, which is not described as the standard approach by the company and there were no histological biopsies performed to assess the achieved tissue quality of the described technique. Fourth, this trial did not clarify whether large cartilage lesions (greater than 6 cm2) can be treated sufficiently by the minced cartilage technique or need to be enhanced by biomaterials or autologous agents. However, data regarding the minced cartilage technique is limited, especially regarding

the whole autologous procedure in combination with PRP; thus, the findings of this trial could add important knowledge to the topic of surgical cartilage treatment.

Hydrogel-Enhanced Autologous Chondrocyte Implantation for Cartilage Repair

Ahmadpoor et al (2024) stated that ACI and MACI have shown improved clinical outcomes and reduced revision rates for treating osteochondral and chondral defects; however, their ability to achieve lasting, fully functional repair remains limited. To overcome these challenges, scaffold-enhanced ACI, especially the sue of hydrogel-based biomaterials, has emerged as an innovative strategy. These biomaterials are intended to mimic the biological composition, structural organization, as well as biomechanical properties of native articular cartilage. These researchers provided comprehensive and up-to-date information regarding advancements in hydrogel-enhanced ACI from the last 10 years. They discussed cartilage biology, mechanisms of cartilage injury, and the evolution of surgical techniques, especially looking at ACI. Subsequently, these investigators reviewed the diversity of hydrogel scaffolds currently undergoing development and evaluation in pre-clinical studies for articular cartilage regeneration, emphasizing chondrocyte-laden hydrogels applicable to ACI. Lastly, the authors addressed the key challenges impeding effective clinical translation, with special attention to issues surrounding fixation and integration, aiming to inform and guide the future progression of tissue engineering strategies. These researchers stated that by overcoming the barrier of integration, hydrogel-based scaffolds hold tremendous promise for advancing ACI techniques and offer viable solutions for cartilage repair in multiple joint applications in clinical settings.

The authors noted that ACI and MACI present a promising approach for treating cartilage injury across various joints, including the knee, hip, shoulder, and ankle; however, significant challenges remain. A primary concern is the current limitation of hydrogels in mimicking the viscoelastic properties of native cartilage, which is crucial for diverse joint applications. Many hydrogels fail to replicate the zonal architecture and complex collagen network inherent in native cartilage, affecting their ability to endure repetitive loading in different joint environments. This

discrepancy could result in inadequate load-bearing capacity and potential delamination at the interface between the hydrogel and native tissue, a risk especially pertinent to weight-bearing joints. Moreover, these researchers stated that each biomaterial holds promise for ACI surgery; however, further optimization is needed to address their limitations and enhance their reparative potential.

Karami et al (2024) stated that knee cartilage has limited natural healing capacity, complicating the development of effective treatment plans. Current non-cell-based therapies (e.g., microfracture) result in poor repair cartilage mechanical properties, low durability, and sub-optimal tissue integration. Advanced treatments, such as ACI, face challenges including cell leakage and inhomogeneous distribution. Successful cell therapy relies on prolonged retention of therapeutic biologicals at the implantation site; however, the optimal integration of implanted material into the surrounding healthy tissue remains an unmet need. In a proof-of-concept (POC) study, these researchers examined the effectiveness of a newly developed photo-curable adhesive hydrogel for cartilage repair, focusing on adhesion properties, integration performance, as well as its ability to support tissue regeneration. The proposed hydrogel design demonstrated significant adhesion strength, out-performing commercial adhesives such as fibrin-based glues. An in-vivo goat model was employed to assess the hydrogels' adhesion properties and long-term integration into full-thickness cartilage defects over 6 months. Results revealed that cell-free hydrogel-treated defects achieved superior integration with surrounding tissue and enhanced cartilage repair, with notable lateral integration. In addition, in-vitro results showed high cell viability, robust matrix production, as well as successful cell encapsulation within the hydrogel matrix. The authors concluded that these preliminary findings revealed the potential of adhesive hydrogel formulations to improve the effectiveness of cell-based therapies, offering a potentially superior treatment for knee cartilage defects. Moreover, these investigators stated that their future studies will focus on establishing a cell-based therapeutic protocol using human cells via comprehensive in-vitro and in-vivo investigations to validate the hydrogel’s safety and effectiveness in cartilage repair.

Periosteal Patch Attachment to Knee Chondral Defects in Autologous Chondrocyte Implantation

Orfanos et al (2024) noted that traditional ACI entails arthroscopically harvesting a cartilage biopsy (stage 1), followed by arthrotomy 3 to 4 weeks later to apply a periosteal patch and implant culture-expanded chondrocytes underneath (stage 2). In a single-center RCT, these researchers examined if patch application during stage 1 rather than stage 2 would improve clinical outcome. This trial was carried out from 1998 to 2001. Patients were randomized to receive either traditional ACI (control/late) or ACI with "early" patch during stage 1 (intervention/early). Clinical outcome (Lysholm score) was assessed pre-operatively and annually post-operatively. A total of 77 patients were recruited, with 40 patients randomized to the early and 37 to the late patch group. The overall mean pre-operative Lysholm score was 51.8 (range of 11 to 89) and significantly improved by 11.1 points (95 % CI: 4.8 to 17.4) at mean 12.7 years (range of 1.5 to 23.7) follow-up. Latest mean Lysholm scores for the early and late groups were 68.4 (95 % CI: 19 to 100) versus 56.7 (95 % CI: 18 to 98). Adjusted for co-variate imbalances, no evidence was found for a difference between the groups (MD = 8.5, 95 % CI: -5.2 to 22.2, p = 0.22); 20-year survival until any re-operation or arthroplasty was 59.6 %/82.1 % for the early and 56.8 %/69.5 % for the late group, with no evidence for a difference. The authors concluded that ACI was an effective durable treatment for cartilage defects, with high levels of patient satisfaction and low failure rates. However, no evidence was found that applying the periosteal patch at the time of chondrocyte harvest improved long-term Lysholm scores or survival until any re-operation or arthroplasty.

The authors stated that this trial had several drawbacks. First, the lack of balance between the groups. Although the randomization used stratification by location and did indeed achieve balance in this characteristic, other characteristics such as age and baseline Lysholm scores showed severe imbalance. Severe imbalance is almost inevitable in small trials, which these investigators tried to prevent by using stratified randomization. However, the number of patients with patellar/trochlear defects was small; thus, the effect of stratification on reducing imbalance was also small, and this may explain the large imbalance in other predictors. A better strategy would have been to include the baseline

Lysholm score, with 2 strata split by the expected median baseline Lysholm score, a strategy these researchers employed in the later trial. However, by doing additional regression analyses using the unbalanced variables (such as Lysholm score) as co-variates, the authors had essentially addressed this design issue at the analysis stage. Second, this trial was also a single-center study with the majority of patients being treated by a single surgeon. This rendered it susceptible to selection bias. Third, these researchers were unable to determine the type of surgical procedure to the defect before ACI. However, because the number of prior procedures was reasonably balanced between the 2 groups, these investigators did not expect this to have introduced a bias. Fourth, with the development of new generations of patch surfaces being used, the results using those should be tested in a similar fashion to confirm these observations.

Appendix

*BMI is calculated by dividing the person's weight (in kilograms) by height (in meters) squared:

BMI = weight (kg) * [height (m)]^2

Note: To convert pounds to kilograms, multiply pounds by 0.45. To convert inches to meters, multiply inches by 0.0254.

or

For a simple and rapid calculation of BMI, please click below and it will take you to the Obesity Education Initiative.

*Body Mass Index Calculator (https://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm)

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