IQWiG Reports – Commission No. N19-02

Autologous chondrocyte implantation in the knee joint[1]

Extract

[1] Translation of Chapters 1 to 6 of the final report N19-02 *Autologe Chondrozytenimplantation am Kniegelenk* (Version 1.1; Status: 3 November 2020 [German original], 01 April 2021 [English translation]). Please note: This document is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Autologous chondrocyte implantation in the knee joint

Commissioning agency:
Federal Joint Committee

Commission awarded on:
25 July 2019

Internal Commission No.:
N19-02

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A8 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

- Nicole Skoetz, University Hospital Cologne, Cologne, Germany
- Alfred Hochrein, OCM Hospital, Munich, Germany

IQWiG thanks the external experts for their collaboration in the project.

IQWiG employees

- Gunnar Plinke
- Moritz Felsch
- Daniel Fleer
- Wolfram Groß
- Inga Overesch

Keywords: Knee Injuries, Transplantation – Autologous, Chondrocytes, Benefit Assessment, Systematic Review

Key statement

Research question

The aim of the present investigation is the benefit assessment of the method of autologous chondrocyte implantation (with a periosteal flap, collagen-covered, matrix-induced) compared with standard treatment in adult patients with a specific symptomatic cartilage defect of the knee without advanced osteoarthritis. The focus of the assessment was on patient-relevant outcomes.

Conclusion

When all 3 procedures of autologous chondrocyte implantation are considered together (matrix-induced [M-ACI], collagen-covered [ACI-C], with a periosteal flap [ACI-P]), the data provide no hint of benefit or harm versus standard treatment for any of the outcomes. At the medium-term time of analysis (11 to 24 months), heterogeneity between ACI procedures was evident for a large proportion of results, so each was considered separately

In the 7 studies comparing M-ACI with standard treatments, beneficial effects in favour of M-ACI were shown for the outcomes of function and health-related quality of life. Although the effects do not reach a clinically relevant magnitude, together with a qualitative examination of all other outcomes it can be assumed that M-ACI has a benefit at least comparable to that of current standard treatments.

Within each of the 2 studies comparing ACI-C and ACI-P with standard treatments, 1 study showed a statistically significant effect in favour of ACI-C for 1 outcome (treatment failure). However, no data on the harm of ACI-C are available from the studies, and all other outcomes on both ACI procedures show partly numerically inconsistent results. Therefore, the data provide no hint of a benefit or harm of ACI-C and ACI-P, and it cannot be estimated with sufficient certainty whether there is a benefit comparable to that of standard treatment.

The results of the 3 studies comparing the ACI procedures in pairs do not contradict the assessment presented above.

Table of contents

Page

Key statement ... **iii**
List of tables ... **vi**
List of abbreviations ... **vii**
1 Background ... **1**
2 Research question ... **3**
3 Methods ... **4**
4 Results ... **6**
4.1 Results of information retrieval ... **6**
4.2 Characteristics of the studies included in the assessment (ACI versus standard treatment) ... **7**
4.3 Overview of patient-relevant outcomes (ACI versus standard treatment) ... **7**
4.4 Assessment of the risk of bias of results (ACI versus standard treatment) ... **8**
4.5 Results on patient-relevant outcomes (ACI versus standard treatment) ... **9**
4.5.1 Results on mortality ... 9
4.5.2 Results on pain ... 10
4.5.3 Results on symptoms ... 10
4.5.4 Results on activities of daily living ... 11
4.5.5 Results on function ... 11
4.5.6 Results on the algofunctional global score ... 12
4.5.7 Results on SAEs ... 13
4.5.8 Results on discontinuation due to AEs ... 13
4.5.9 Results on treatment failure ... 14
4.5.10 Results on health-related quality of life ... 14
4.5.11 Sensitivity and subgroup analyses ... 15
4.6 Characteristics and results of the studies comparing different ACI variants ... **16**
4.7 Summary of results ... **17**
4.8 Evidence map ... **19**
5 Classification of the assessment result ... **20**
6 Conclusion ... **22**
References for English extract ... **24**
Appendix A – Search strategies ... **31**
A.1 – Searches in bibliographic databases ... **31**
A1.1.1 Systematic reviews ... 31

A.2 – Searches in study registries..... 34

List of tables

Page

Table 1: Study pool of the benefit assessment 6
Table 2: Matrix of patient-relevant outcomes on the comparison of ACI versus standard treatment 8
Table 3: Matrix of the patient-relevant outcomes of the studies comparing different ACI variants 17
Table 4: Evidence map in relation to patient-relevant outcomes 20

List of abbreviations

Abbreviation	Meaning
ACI	autologous chondrocyte implantation
ACI-C	collagen-covered autologous chondrocyte implantation
ACI-P	autologous chondrocyte implantation with a periosteal flap
AE	adverse event
AMG	Arzneimittelgesetz (German Medicines Act)
ATMP	Advanced Therapeutical Medicinal Products
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IKDC	International Knee Documentation Committee
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
KOOS	Knee Injury and Osteoarthritis Outcome Score
M-ACI	matrix-induced autologous chondrocyte implantation
MD	mean difference
MF	microfracturing
OR	odds ratio
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

Autologous chondrocyte implantation (ACI) is a 2-step surgical procedure for the treatment of symptomatic isolated cartilage defects in the knee in adults. Depending on activity level and age, the procedure is used from a cartilage defect size of 2.5 cm² upwards [1]. In young active adults, a cartilage defect is usually caused by a sports injury [2]. The classification system of the International Cartilage Repair Society (ICRS) comprises 4 grades of severity and is routinely used to determine the grade of severity of a cartilage defect [3]. The ACI is indicated for grades 3 and 4 and thus includes cartilage defects that affect more than 50% of the cartilage depth, as well as defects extending into the underlying bone. An advanced degenerative joint disease is the most important contraindication [1]. ACI has been used for over 30 years and been further developed and modified over time [4].

In ACI, cartilage is removed during an initial operation and the cartilage cells are isolated and cultivated in a laboratory. These cartilage cells are then reimplanted into the defect. The method can basically be classified into 3 procedures, which differ in the approach for the reimplantation of the cultivated cells into the cartilage defect area [5]. These 3 procedures are all subject of the benefit assessment.

In first-generation ACI, ACI with a periosteal flap (ACI-P), the cultivated cartilage cells are reimplanted into the cartilage defect area in the form of a cell suspension and covered using the patient's periosteum. In second-generation ACI, a collagen cover (collagen-covered ACI, ACI-C) replaces the periosteal flap. In both procedures, the cover must be fixed with seams and a watertight sealing. The latest development (third generation) is the matrix-induced ACI (M-ACI). The cultivated cartilage cells are directly fixed on a carrier matrix and reimplanted into the cartilage defect area [4]. In M-ACI, there are different procedures with regard to the structure of the matrix and the selection of cartilage cells [5].

In 2007, about 800 cases were billed for M-ACI in Germany according to the OPS[2]. In the following years, the number of cases rose steadily to more than 2700 cases in 2015. In 2005, more than 650 cases were billed for the two older procedures ACI-P and ACI-C according to the OPS. In 2015, however, only around 120 of these operations were billed [6].

Cartilage tissue has only a very limited regenerative capacity and a cartilage defect represents a risk factor for the development of osteoarthritis. Conservative treatment methods such as physiotherapy have not yet been shown to affect the course of disease. Most cases, especially larger cartilage defects, are therefore regarded as an indication for surgical cartilage therapy [7].

Other surgical treatment options for cartilage defects on the knee include methods that stimulate the bone marrow (microfracturing [MF], abrasion arthroplasty, and drilling techniques) and –

[2] *Operationen- und Prozedurenschlüssel* (Operating and Procedure Code)

in addition to ACI – other transplantation methods (osteochondral transplantation [OCT], osteochondral autologous transplantation system [OATS], and mosaicplasty [MP]) [1]. ACI is an established procedure in German health care. Nevertheless, only the above-mentioned surgical treatment options are referred to as standard treatment in this report, as this term corresponds to the original name in the G-BA commission for the comparator therapy.

2 Research question

The aim of the present investigation is

- the benefit assessment of the method of autologous chondrocyte implantation (with a periosteal flap, collagen-covered, matrix-induced) compared with standard treatment

in adult patients with a specific symptomatic cartilage defect of the knee without advanced osteoarthritis. The focus of the assessment was on patient-relevant outcomes.

3 Methods

The target population for the benefit assessment were adult patients with a specific symptomatic cartilage defect of the knee without advanced osteoarthritis. The test intervention was ACI in the knee (with a periosteal flap, collagen-covered, matrix-induced). The control interventions were all interventional standard treatments.

The following patient-relevant outcomes were considered in the investigation:

- mortality
- morbidity (e.g. renewed surgery, pain, avoidance of osteoarthritis and joint replacement, knee function, movement range, activity level)
- health-related quality of life
- adverse events

Only randomized controlled trials (RCTs) with a follow-up period of at least 6 months were included in the benefit assessment.

To prepare for the comprehensive information retrieval, a search for systematic reviews was conducted in MEDLINE and the Cochrane Database of Systematic Reviews as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ). The search was restricted to articles published from January 2014 onwards. A systematic search for primary studies was conducted in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

In addition, the following information sources and search techniques were considered: study registries, enquiries to manufacturers, publicly accessible documents of regulatory authorities, documents transferred by the G-BA, reference lists, and documents and enquiries to authors provided in hearing procedures.

The selection of relevant studies within the framework of comprehensive information retrieval was conducted by 3 persons independently of one another. The results of study selection were summarized after the assessment of full texts. Data were extracted into standardized tables. To evaluate the qualitative certainty of results, criteria across outcomes and outcome-specific criteria for the risk of bias were rated and, in each case, classified as low or high. The results of individual studies were organized and described according to outcomes.

In addition to the comparison of the results of individual studies, meta-analyses and sensitivity analyses were performed and effect modifiers investigated, provided the methodological preconditions were fulfilled. A concluding summarizing assessment was always performed.

For each outcome, a conclusion on the evidence base of the (greater) benefit and (greater) harm was drawn in 4 levels with regard to the respective certainty of the conclusion: The data

provided either “proof” (highest certainty of conclusions), an “indication” (medium certainty of conclusions), a “hint” (weakest certainty of conclusions), or none of these 3 situations applied. The latter was the case if no data were available or the data available did not allow any of the other 3 conclusions to be drawn. In this case, the following conclusion was drawn: “the data provide no hint of (greater) benefit or (greater) harm”.

The ACI procedures were initially examined across procedures. For all outcomes, a stratified meta-analytical presentation was displayed according to the ACI procedure (matrix-induced, collagen-covered, with a periosteal flap), independently of the heterogeneity observed between the ACI procedures. If the results indicated that the benefit of individual ACI procedures differed, the study pools of the individual procedures were evaluated separately and studies comparing the procedures with each other were also examined.

For all outcomes, the evaluable data were extracted for the short-term (3 months), medium-term (18 to 24 months) and long-term (60 months) time of analysis. If data on an outcome were only available at 11, 12 or 36 months, they were assigned to the medium-term time of analysis. If several data were available within the time of analysis categories, they were only to be presented if there was a relevant difference in results. This was not the case in the present assessment. Results on very long follow-up periods (10 and 15 years) were available for the outcome of treatment failure and were analysed for the report.

4 Results

4.1 Results of information retrieval

Information retrieval identified 16 RCTs as relevant for the research question of the present benefit assessment (Table 1).

Table 1: Study pool of the benefit assessment

Study	Available documents		
	Full publications (in scientific journals)	**Registry entry / Results report from study registries**	**Study report from manufacturer documents (not publicly accessible)**
Comparison ACI versus standard treatment			
Basad 2004	yes [10,25]	no / no	no
Bentley 2003	yes [17,26]	no / no	no
Clavé 2016	yes [11]	yes [27] / no	no
cod16HS13	yes [12,28]	yes [29-31] / no	yes [32]
Crawford 2012	yes [13,33]	yes [34] / no	no
Dozin 2012[a]	yes [8]	no / no	no
Fossum 2019	yes [18]	yes [35] / no	no
Knutsen 2004	yes [19,36-38]	no / no	no
Lim 2012[a]	yes [9]	no / no	no
MACI00206	yes [14,39]	yes [40,41] / yes [42,43]	no
	yes[b] [44]	yes[b] [45,46] / yes[b] [47,48]	no
TIGACT01	yes [20,49-51]	yes [52] / yes [53]	no
Visna 2004	yes [15]	no	no
Yoon 2020	yes [16]	yes [54,55] / no	no
Comparison ACI versus ACI			
Bartlett 2005	yes [21]	no	no
Gooding 2006	yes [22]	no	no
Zeifang 2010	yes [23]	no	no

a. No consideration of outcomes for the assessment because it is based on less than 70% of the data from the patients to be included in the analysis.
b. Extension study.
ACI: autologous chondrocyte implantation

Two studies (Dozin 2005 und Lim 2012 [8,9]) were included as they fulfilled all inclusion criteria; however, they did not provide evaluable results for any patient-relevant outcome. The study pool thus contained a total of 14 studies reporting evaluable data on patient-relevant outcomes.

A total of 11 studies compared ACI and standard treatment. The corresponding results are presented in the following Sections 4.2 to 4.5. The characteristics and results of the 3 studies comparing different ACI variants are presented in Section 4.6.

Seven ongoing studies were identified. Furthermore, 3 studies with an unclear status, as well as 2 discontinued and 1 completed study without reported results, were identified.

The search strategies for bibliographic databases and study registries are included in Appendix A. The last comprehensive search was conducted on 15 October 2019 and the focussed update search was conducted on 18 June 2020.

One study included without reported results [24] investigated M-ACI versus standard treatment with a total of 48 randomized patients. The study had been completed more than 2 years before the present report was prepared (see also Chapter 5).

4.2 Characteristics of the studies included in the assessment (ACI versus standard treatment)

The 11 RCTs comparing ACI and standard treatment and reporting evaluable results for the benefit assessment provided data on about 800 patients. The studies were mainly conducted in Europe. These 2-arm studies randomized between 30 and 144 patients and were conducted between 1999 and 2018 (except for 1 study, where results are expected later). The follow-up period was between 11 months and 15 years. The studies included patients aged 16 to 65 with cartilage defect sizes between 1 und 10 cm^2. In nearly all studies, the majority of participants were men. All studies investigated the treatment of cartilage defects with the ICRS or Outerbridge grades of severity 3 and 4. All studies referred to the inpatient health care sector.

4.3 Overview of patient-relevant outcomes (ACI versus standard treatment)

Data on patient-relevant outcomes were extracted from 11 studies.

Table 2 shows the overview of patient-relevant outcomes from the studies with evaluable results on the comparison of ACI versus standard treatment.

Table 2: Matrix of patient-relevant outcomes on the comparison of ACI versus standard treatment

Study	Outcomes									
	Mortality	Morbidity								QoL
	Overall mortality	Pain	Symptoms	Activities of daily living	Function	Algofunctional global score	SAEs	Discontinuation due to AEs	Treatment failure[a]	Health-related quality of life
M-ACI versus standard treatment										
Basad 2004	–	–	–	–	●	●	●	–	–	–
Clavé 2016	–	–	–	–	–	●	–	–	–	–
cod16HS13	●	●	●	●	●	●	●	●	●	●
Crawford 2012	–	●	x	x	x	●	●	●	–	x
MACI00206	●	●	●	●	●	●	●	●	●	●
Visna 2004	–	–	–	–	○[b]	●	–	–	–	–
Yoon 2020	–	●	●	●	●	●	–	–	–	●
ACI-C versus standard treatment										
Bentley 2003	–	–	–	–	–	●	–	–	●	–
Fossum 2019	–	●	●	●	●	●	–	–	●	●
ACI-P versus standard treatment										
Knutsen 2004	–	●	–	–	●	●	–	–	●	●
TIGACT01	–	●	●	●	x	–	●	●	●	●

●: Data were reported and were evaluable.
○: Data were reported, but were not evaluable for the benefit assessment.
x: Data were not reported, despite the fact that data collection was planned.
–: No data were reported (no further information). / The outcome was not recorded.
a. Treatment failure was defined by a validated patient questionnaire or the need for reintervention.
b. The proportion of patients who were not included in the analysis is greater than 30%.

AE: adverse event; ACI: autologous chondrocyte implantation; ACI-C: collagen-covered autologous chondrocyte implantation; ACI-P: autologous chondrocyte implantation with a periosteal flap; M-ACI: matrix-induced autologous chondrocyte implantation; QoL: health-related quality of life; SAE: serious adverse event

4.4 Assessment of the risk of bias of results (ACI versus standard treatment)

The risk of bias across outcomes of the results on the comparison of ACI versus standard treatment was rated as high for 7 studies (Basad 2004, Crawford 2012, Visna 2004, Yoon 2020,

Bentley 2003, Fossum 2019, Knutsen 2004). This was due to the inadequate description of allocation concealment and, in part, possible concurrent selective outcome reporting.

For the 4 studies with a low risk of bias across outcomes (Clavé 2016, cod16HS13, MACI00206, TIGACT01), the outcome-specific risk of bias of the results was assessed. In the remaining 7 studies, the high risk of bias across outcomes translated directly into a high outcome-specific risk of bias of the results.

For the studies Clavé 2016, cod16HS13, MACI00206, and TIGACT01, a high outcome-specific risk of bias was found for all outcomes assessed by questionnaire (pain, symptoms, activities of daily living, function, algofunctional global score, and health-related quality of life) due to the open study design and a partial violation of the intention-to-treat (ITT) principle.

For the cod16HS13 study, the risk of bias for the outcomes of serious adverse events (SAEs), discontinuation due to adverse events (AEs), and treatment failure was rated as high for all times of analyses due to unclear implementation of the ITT principle.

For the MACI00206 study, the risk of bias was low for the outcome of SAEs. For the outcome of discontinuation due to AEs, the risk of bias was rated as high, as it was unclear whether some of the discontinuations were also due to non-serious AEs. Thus, there is a risk of bias due to subjective reasons for discontinuation in the context of the open study design. For the outcome of treatment failure, the risk of bias was rated as high, as the assessment of treatment failure and the need for re-intervention were subjective in the context of the open study design.

For the TIGACT01 study, the risk of bias was high for the outcome of SAEs due to the violation of the ITT principle. For the outcome of discontinuation due to AEs, the risk of bias was rated as high, as it was unclear whether some of the discontinuations were also due to non-serious AEs. Thus, there is a risk of bias due to subjective reasons for discontinuation in the context of the open study design. For the outcome of treatment failure, there was a high risk of bias, as the assessment of treatment failure and the need for re-intervention were subjective in the context of the open study design.

The risk of bias for the outcome of mortality was not assessed due to only 1 death in 1 treatment arm of a study.

4.5 Results on patient-relevant outcomes (ACI versus standard treatment)

4.5.1 Results on mortality

Overall, for the outcome of mortality, data were available from only 2 of the 11 studies. In the MACI00206 study (N = 144), no deaths occurred at 24 months. In the cod16HS13 study (N = 102), there was 1 death in the control group (n = 50) at 36 months.

Thus, for the outcome of mortality, the data provide no hint of a benefit or harm of ACI versus standard treatment.

4.5.2 Results on pain

Overall, for the outcome of pain, data with a moderate certainty of results were available from 7 studies on the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale “pain” and the visual analogue scale (VAS).

For M-ACI, data were available from 2 studies at the short-term, 4 studies at the medium-term, and 1 study at the long-term time of analysis. For ACI-C, data from 1 study were available for the medium-term time of analysis. For ACI-P, data were available from 2 studies for the medium- and long-term times of analysis.

When the meta-analyses across procedures were examined, no statistically significant effect could be shown at any time of analysis.

For the medium-term time of analysis, there was a statistically significant interaction between the ACI procedures ($p = 0.013$). Although the contrasting location of the effect estimates suggests that the effect of M-ACI differs from that of the other procedures, no hint of an effect could be derived for any of the procedures.

For the long-term time of analysis, there was no statistically significant interaction between the ACI procedures ($p = 0.513$). If the procedures would nevertheless be examined separately, there would be no hint of an effect here either.

Overall, for the outcome of pain, the data provide no hint of a benefit or harm of ACI procedures versus standard treatment.

4.5.3 Results on symptoms

Overall, for the outcome of symptoms, data with a moderate qualitative certainty of results were available from 5 studies on the KOOS subscale “symptoms”.

For M-ACI, data were available from 1 study at the short-term, 3 studies at the medium-term, and 1 study at the long-term time of analysis. For ACI-C, data from 1 study were available at the medium-term time of analysis; for ACI-P, data from 1 study were available at the medium-term and long-term times of analysis.

No hint of an effect could be derived from either the examination of the single study at the short-term time of analysis or the meta-analyses across procedures at the medium- and long-term times of analysis.

At the medium-term time of analysis, there was a statistically significant interaction between the ACI procedures ($p = 0.033$). Although the contrasting location of the effect estimates suggests that the effect of M-ACI differs from that of the other procedures, no hint of an effect could be derived for any of the procedures.

At the long-term time of analysis, there was no statistically significant interaction between the ACI procedures (p = 0.889). If both procedures were nevertheless examined separately, there was no hint of an effect.

Overall, for the outcome of symptoms, the data provide no hint of a benefit or harm of ACI procedures versus standard treatment.

4.5.4 Results on activities of daily living

Overall, for the outcome of activities of daily living, data with a moderate qualitative certainty of results were available from 5 studies on the KOOS subscale “activities of daily living”.

For the M-ACI, data were available from 1 study at the short-term, 3 studies at the medium-term, and 1 study at the long-term time of analysis. For the ACI-C, data from 1 study were available for the medium-term time of analysis. For ACI-P, data were available from 1 study at the medium- and long-term times of analysis.

No hint of an effect could be derived from either the examination of the single study at the short-term time of analysis or the meta-analysis across procedures at the long-term time of analysis. Results at the medium-term time of analysis showed relevant heterogeneity between studies across procedures (p = 0.006). Therefore, no overall meta-analysis estimate was calculated. No hint of an effect could be derived from a qualitative analysis either.

For the medium-term time of analysis, there was a statistically significant interaction between the ACI procedures (p = 0.016). However, no hint of an effect could be derived for the individual procedures. For the long-term time of analysis, there was no statistically significant interaction between the ACI procedures (p = 0.802). If the procedures would nevertheless be examined separately, there would be no hint of an effect here either.

Overall, for the outcome of activities of daily living, the data provide no hint of a benefit or harm of any of the ACI procedures versus standard treatment.

4.5.5 Results on function

For the outcome of function, data with a moderate qualitative certainty of results were available from 6 studies, collected with the KOOS subscale “physical activity” and the Tegner score.

For M-ACI, data were available from 1 study at the short-term, 4 studies at the medium-term, and 1 study at the long-term time of analysis. Data from 1 study each were available for the medium-term time of analysis (for ACI-C) and for the long-term time of analysis (for ACI-P).

When examining the single study at the short-term time of analysis, no hint an effect could be derived. For the medium- and long-term time of analysis, Hedges’ g was used as the effect estimate, as scales with different levels of measurement were used in the studies to determine this outcome (Tegner score and KOOS subscale “physical activity”). In the analysis across

procedures at the medium-term time of analysis, no overall estimator was presented due to relevant heterogeneity between the studies (p = 0.034). No hint of an effect could be derived from a qualitative analysis either. In the meta-analysis across procedures at the long-term time of analysis, no hint of an effect could be derived either.

The results for the medium-term time of analysis showed relevant heterogeneity between the procedures (p = 0.004). The study on ACI-C showed no statistically significant difference. The meta-analysis of the 4 studies on the M-ACI procedure showed a statistically significant effect (p = 0.015) in favour of the intervention. However, the threshold for clinical relevance (0.2) is within the confidence interval (CI) of the pooled effect (Hedges' g: 0.46; 95% CI: [0.17; 0.76]). Thus, the effect for M-ACI does not reach a clinically relevant magnitude.

Overall, for the outcome of function, the data provide no hint of a benefit or harm of any of the ACI procedures versus standard treatment.

4.5.6 Results on the algofunctional global score

Questionnaires representing multiple domains such as function, pain and symptoms in a total score were assigned to the outcome referred to in this report as the "algofunctional global score".

For the outcome "algofunctional global score", data with a moderate qualitative certainty of results were available from 10 studies.

A total of 9 studies reported, among others, results on mean differences in the International Knee Documentation Committee (IKDC) Subjective Knee Form and the Lysholm score. For M-ACI, data were available from 4 studies at the short-term, 7 studies at the medium-term, and 1 study at the long-term time of analysis. For ACI-C, data were available from 1 study for the medium-term time of analysis; for ACI-P, data were available from 1 study each for the medium- and long-term times of analysis.

In the meta-analyses across procedures of the results on mean differences, no hint of an effect could be derived for any of the times of analysis.

For the medium-term time of analysis, there was no statistically significant interaction between the ACI procedures (p = 0.106). Nevertheless, when examined separately, there was significant heterogeneity (p = 0.002) within the M-ACI studies. There was no hint of an effect for any of the procedures. In a sensitivity analysis of the studies comparing M-ACI with MF, there was no statistically significant difference between the groups either. For the long-term time of analysis, there was no statistically significant interaction between the ACI procedures (p = 0.148). If the procedures would nevertheless be examined separately, there would be no hint of an effect here either.

Three studies reported results from responder analyses at medium- and long-term times of analysis, defined by change thresholds or target scores of the following scales applied: KOOS

(2 subscales: “pain” and “sport and recreation function”), IKDC Subjective Knee Form, and the modified Cincinnati Rating System.

The meta-analytic summary across procedures of the 3 studies at the medium-term time of analysis showed a statistically significant effect in favour of the ACI procedures (odds ratio [OR]: 3.01; 95% CI: [1.56; 5.82]; p-value: 0.019). However, corresponding responder analyses providing results based on the mean difference are missing for 6 of the studies. This also includes the Clavé 2016 study, which showed a statistically significant effect in favour of standard treatment (mosaicplasty). As the study pool is thus incomplete compared to the study pool with mean differences, these results cannot be used. The only study for the long-term time of analysis (MACI00206) showed no statistically significant effect.

Overall, for the outcome “algofunctional global score”, the data provide no hint of a benefit or harm of ACI procedures versus standard treatment.

4.5.7 Results on SAEs

For the outcome of SAEs, data were available from 5 studies, of which 1 study had high and 4 studies had a moderate qualitative certainty of results. The study with a high qualitative certainty of results did not show a statistically significant effect and was therefore not examined separately.

For M-ACI, data from 4 studies were available at the medium-term time of analysis; for ACI-P, data from 1 study were available at the medium- and long-term times of analysis.

When examining the meta-analysis across procedures, no statistically significant effect could be shown for the medium-term time of analysis. There was no statistically significant interaction between the ACI procedures ($p = 0.778$). If the procedures would nevertheless be examined separately, there would be no hint of an effect here either. The single study at the long-term time of analysis showed no statistically significant effect.

Overall, for the outcome of SAEs, the data provide no hint of a benefit or harm of ACI procedures versus standard treatment.

4.5.8 Results on discontinuation due to AEs

Overall, for the outcome of discontinuation due to AEs, data were available from 4 studies with a moderate qualitative certainty of results.

For M-ACI, 3 studies were available and for ACI-P, 1 study was available at the medium-term time of analysis.

No statistically significant effect could be shown in the meta-analysis across procedures. Due to the low number of events, a separate analysis of the ACI procedures was not meaningful.

Overall, for the outcome of discontinuation due to AEs, the data provide no hint of a benefit or harm of ACI procedures versus standard treatment.

4.5.9 Results on treatment failure

The results on treatment failure from the studies were considered if treatment failure was defined either by a validated questionnaire on patients' subjective complaints or included the need for a re-intervention.

For the outcome of treatment failure, data were available from 6 studies with a moderate qualitative certainty of results.

For M-ACI, data were available from 2 studies at the medium-term time of analysis and from 1 study at the long-term time of analysis. For ACI-C, data were available from 1 study each at the medium-term and long-term times of analysis. For ACI-P, data were available from 2 studies each at the medium-term and long-term times of analysis.

In the meta-analyses across procedures, no statistically significant effect could be shown for the medium- and long-term times of analysis. For both times of analysis, there was no statistically significant interaction between the procedures (medium-term: $p = 0.256$; long-term: $p = 0.405$). If the procedures would nevertheless be examined separately, there would be no hint of an effect for any of the procedures.

The two studies with a particularly long follow-up, Bentley 2003 (10 years) and Knutsen 2004 (15 years), were examined separately. In the Bentley 2003 study, there was a statistically significant effect in favour of ACI-C (OR: 0.17; 95% CI: [0.07; 0.43]; p-value: < 0.001). For ACI-P, there was no statistically significant effect at 180 months in the Knutsen 2004 study.

Overall, for the outcome of treatment failure, the data provide no hint of a benefit or harm of the M-ACI and ACI-P procedures versus standard treatment. For the ACI-C procedure, the data provide a hint of a benefit for this outcome.

4.5.10 Results on health-related quality of life

Overall, for the outcome of health-related quality of life, data with a moderate qualitative certainty of results were available from 6 studies on the KOOS subscale "quality of life" and the physical summary score of the Health Survey Short Form 36 (SF-36).

For M-ACI, data were available from 1 study at the short-term, 3 studies at the medium-term, and 1 study at the long-term time of analysis. For ACI-C, data from 1 study were available for the medium-term time of analysis; for ACI-P, data from 2 studies each were available for the medium- and long-term times of analysis.

At the short-term time of analysis, the cod16HS13 study showed a statistically significant effect in favour of M-ACI (mean difference [MD]: 9.30; 95% CI: [1.02; 17.58]; p-value: 0.028).

However, the threshold for clinical relevance (Hedges'g ≥ 0.2) was within the confidence interval of the effect (Hedges'g: 0.45; 95% CI: [0.05; 0.85]). Thus, the effect for M-ACI did not reach a clinically relevant magnitude.

The results at the medium-term time of analysis showed relevant heterogeneity across procedures (p = 0.026). Therefore, no overall estimator of the meta-analysis was calculated. No hint of an effect could be derived from a qualitative analysis either. There was a statistically significant interaction between the ACI procedures (p = 0.006). The meta-analysis of the 3 studies on the M-ACI procedure showed a statistically significant effect in favour of the intervention (MD: 9.22; 95% CI: [1.00; 17.44]; p-value: 0.040). However, the effect did not reach a clinically relevant magnitude, as the result on effect size using Hedges'g was not statistically significant (Hedges'g: 0.38; 95% CI: [-0.01; 0.77]). Examined separately, the data provide no hint of an effect at the medium-term time of analysis for the ACI-C and ACI-P procedures.

The meta-analysis across procedures at the long-term time of analysis did not show a statistically significant effect. There was no statistically significant interaction between the ACI procedures (p = 0.220). If the ACI procedures would nevertheless be examined separately, there would be no hint of an effect for either the M-ACI or the ACI-P.

Overall, for the outcome of health-related quality of life, the data provide no hint of a benefit or harm of ACI procedures versus standard treatment.

4.5.11 Sensitivity and subgroup analyses

Sensitivity analyses

For continuous outcomes, the difference in changed values was evaluated in each case. If no changed values were reported in the studies, the difference of the absolute values at the time of analysis was considered. If both changed and absolute values were available for a study, the difference of the absolute values at the times of analysis investigated (short-, medium- and long-term) were evaluated in sensitivity analyses. However, these sensitivity analyses did not show any deviating results and thus had no influence on the derivation of the evidence.

Subgroup analyses

Across studies, no subgroup analysis could be performed for any of the planned subgroup characteristics, as the studies could not be assigned to suitable categories.

In study MACI00206, for the responder analysis (simultaneous improvement of more than 10 points in the 2 KOOS subscales "sport and recreation function" and "pain"), the type of trauma (acute vs. non-acute trauma) was tested for interaction as a potential effect modifier. The test for interaction regarding type of trauma showed statistical significance (p = 0.022). However, no definition of acute trauma was provided and it remained unclear whether the analysis was prespecified. Therefore, this result cannot be used. In addition, no other study examined the type of trauma in terms of subgroup effects. The tests in the MACI00206 study for interaction

regarding sex, age, number of defects, previous cartilage surgery, previous surgery, symptom duration, defect size, trauma localization, and presence of osteochondritis dissecans (OCD) showed no statistical significance.

In the Clavé 2016 study, cartilage defect size ($\leq$ 3.5 versus > 3.5 cm²) was examined as a potential effect modifier for the outcome "algofunctional global score" using the IKDC Subjective Knee Form. The test for interaction with respect to cartilage defect size showed no statistical significance.

4.6 Characteristics and results of the studies comparing different ACI variants

The Bartlett 2005 (M-ACI versus ACI-C), Gooding 2006 (ACI-C versus ACI-P), and Zeifang 2010 (M-ACI versus ACI-P) studies were conducted between 1999 and 2008 in England and Germany and randomized 91, 68, and 21 patients, respectively. The follow-up period was 1 (Bartlett 2005) and 2 years. Cartilage defect sizes between 1 and 22 cm² were treated. The health care sector was exclusively inpatient. An assessment of the risk of bias in these studies was not performed, as a simplified procedure was used to assess only whether their results contradicted the overall view of the studies comparing ACI procedures with standard treatments.

Table 3 shows the summary of available data on patient-relevant outcomes from the studies comparing ACI procedures with each other.

Table 3: Matrix of the patient-relevant outcomes of the studies comparing different ACI variants

Study	Outcomes									
	Mortality	Morbidity								QoL
	All-cause mortality	Pain	Symptoms	Activities of daily living	Function	Algofunctional global score	SAEs	Discontinuation due to AEs	Treatment failure	Health-related quality of life
M-ACI versus ACI-C										
Bartlett 2005	–	●	–	–	–	●	–	–	●	–
ACI-C versus ACI-P										
Gooding 2006	–	–	–	–	–	●	–	–	●	–
M-ACI versus ACI-P										
Zeifang 2010	–	–	–	–	●	●	–	–	–	○

●: Data were reported and were evaluable.
○: Data were reported, but were not evaluable for the benefit assessment.
–: No data were reported (no further information). / The outcome was not recorded.

AE: adverse event; ACI: autologous chondrocyte implantation; ACI-C: collagen-covered autologous chondrocyte implantation; ACI-P: autologous chondrocyte implantation with a periosteal flap; M-ACI: matrix-induced autologous chondrocyte implantation; QoL: health-related quality of life; SAE: serious adverse event

The Bartlett 2005 and Gooding 2006 studies did not show statistically significant differences between the treatment groups for any of the patient-relevant outcomes. The same applied to the outcome of function in the Zeifang 2010 study. However, for the outcome "algofunctional global score", the Zeifang 2010 study showed a statistically significant difference between groups in favour of ACI-P versus M-ACI at 12 months based on the Lysholm score. However, the difference did not reach a clinically relevant magnitude on the basis of testing with the Hedges'g threshold of 0.2 and was no longer statistically significant at the 24-month time of analysis. For the IKDC Subjective Knee Form instrument, which is also attributable to this outcome, there was no statistically significant difference at 12 and 24 months in the same study.

4.7 Summary of results

Across procedures, the data provide no hint of a benefit or harm for the comparison of ACI versus standard treatment for any of the outcomes. At the medium-term time of analysis, questionnaire-based outcomes predominantly showed heterogeneity between ACI procedures, so these were examined separately.

M-ACI versus standard treatment

For the outcome of health-related quality of life, statistically significant effects in favour of the M-ACI procedure versus standard treatment were shown in a single study at the short-term time of analysis and in the meta-analysis at the medium-term time of analysis. For the outcome of function, a statistically significant effect in favour of the M-ACI procedure was shown for the medium-term time of analysis in the meta-analysis. However, the effects of the two outcomes did not reach a clinically relevant magnitude.

For the outcomes of pain and symptoms, no hint of an effect could be derived for M-ACI. However, the location of the effect estimates at the medium-term time of analysis also suggests that the effect of the M-ACI may differ from that of the other ACI procedures. For example, in contrast to the ACI-P and ACI-C procedures, the M-ACI procedure usually showed numerically better results than standard treatment.

The results at other times of analysis and other outcomes of the studies on M-ACI almost without exception point numerically in the direction of an advantage of M-ACI versus standard treatment.

In summary, on the basis of 7 RCTs, M-ACI was found to provide a benefit at least comparable to that of standard treatments.

ACI-C versus standard treatment

The existing evidence on ACI-C is based on 2 RCTs. The Fossum 2019 study numerically indicates an unfavourable effect of ACI-C versus standard treatment for all outcomes except treatment failure. The Bentley 2003 study, although recording only 2 outcomes, shows a numerically (algofunctional global score) and a statistically significant (treatment failure) beneficial effect of ACI-C versus standard treatment. For the outcome of treatment failure, the data provide a hint of a benefit. No data are available on the harm from ACI-C, as neither study reported data on SAEs and discontinuation due to AEs.

In summary, on the basis of the partly numerically inconsistent results of 2 RCTs with a moderate certainty of results and missing data on harms, the data provide no hint of a benefit or harm of ACI-C and it cannot be estimated with sufficient certainty whether there is a benefit comparable to that of standard treatment.

ACI-P versus standard treatment

The available evidence on ACI-P is based on 2 RCTs. The Knutsen 2004 study numerically indicates an unfavourable effect of ACI-P versus standard treatment for all reported outcomes, without exception. The TIGACT01 study has predominantly a numerically opposite result. For instance, it shows a numerically unfavourable effect in the areas of pain, symptoms, and activities of daily living in the medium-term. However, after a long-term follow-up, the estimators are on the side of a numerical advantage for ACI-P versus standard treatment, as is the case for most other outcomes.

In summary, on the basis of the numerically inconsistent results of 2 RCTs with a moderate certainty of results, the data provide no hint of a benefit or harm of ACI-P and it is not possible to assess with sufficient certainty whether there is a benefit comparable to that of standard treatment.

Comparison of different ACI variants

In the 3 RCTs investigating pairwise comparisons of ACI procedures, there is no statistically significant difference between ACI procedures for any outcome except one. Only an interim analysis of the algofunctional global score at the 12-month time of analysis shows a statistically significant difference in favour of ACI-P compared with M-ACI, but this difference does not reach a clinically relevant magnitude and is no longer statistically detectable after 24 months.

Thus, the results from the studies comparing the individual ACI procedures with each other do not contradict the assessment of the benefit and harm of ACI presented in the 3 preceding sections, which result from the examination of studies comparing ACI procedures with standard treatment.

4.8 Evidence map

The following Table 4 shows the evidence map with regard to patient-relevant outcomes.

Table 4: Evidence map in relation to patient-relevant outcomes

Outcome category	Outcome	ACI versus standard treatment	ACI versus ACI
Mortality	Mortality	(⇔)	–
Morbidity	Pain	⇑⇓	M-ACI vs. ACI-C: ⇔
	Symptoms	⇑⇓	–
	Activities of daily living	⇑⇓	–
	Function	⇑⇓[a]	M-ACI vs. ACI-P: ⇔
	Algofunctional global score	⇑⇓	M-ACI vs. ACI-C: ⇔ ACI-C vs. ACI-P: (⇔) M-ACI vs. ACI-P: ⇑⇓[b]
	Treatment failure	⇑⇓[c]	M-ACI vs. ACI-C: (⇔) ACI-C vs. ACI-P: (⇔)
	SAEs	⇔	–
	Discontinuation due to AEs	(⇔)	–
QoL	Health-related quality of life	⇑⇓ [a]	–

⇔: no hint, indication or proof, homogeneous result.
(⇔): no hint, indication or proof, homogeneous result; the 95% confidence interval for the relative effect is so imprecise that neither a halving nor a doubling of the effect can be excluded.
⇑⇓: no hint, indication or proof, heterogeneous result.
–: no (evaluable) data reported.
a. Assumption of at least comparable benefit of M-ACI versus standard treatment (basis: effect in favour of M-ACI, which does not reach a clinically relevant magnitude).
b. For this outcome, the Lysholm score shows a statistically significant difference between the treatment groups in favour of ACI-P after 12 months, which does not reach a clinically relevant magnitude. At the 24-month time of analysis, this is no longer statistically significant. For the IKDC Subjective Knee Form instrument, which was also recorded for this outcome, there was no statistically significant difference after 12 and 24 months.
c. For ACI-C the data provide a hint of a benefit.

AE: adverse event; ACI: autologous chondrocyte implantation; ACI-C: collagen-covered autologous chondrocyte implantation; ACI-P: autologous chondrocyte implantation with a periosteal flap; IKDC: International Knee Documentation Committee; M-ACI: matrix-induced autologous chondrocyte implantation; QoL: health-related quality of life; SAE: serious adverse event

5 Classification of the assessment result

Publication bias

The available information indicates that publication bias is unlikely, as only a negligible amount of data are missing. With the results of 48 individuals from the 017-05-INR study [24], a maximum of 6% of the available data are missing.

Availability of ACI with a periosteal flap and collagen-covered ACI in Germany

ACI products are biotechnologically modified tissue products and belong to the group of Advanced Therapeutical Medicinal Products (ATMPs). For market access on a European level, ATMPs have to undergo a centralized approval procedure according to Regulation (EC) No.

1394/2007 [56]. An exemption regarding the centralized approval requirement exists for ATMPs if the prerequisites according to Section 4b (3) of the German Medicines Act (Arzneimittelgesetz, AMG) are fulfilled. ATMPs are then approved at the national level if, for example, the manufacturer conducts approval studies for the European approval procedure [57,58].

At the time of reporting, only the matrix-induced ACI product from the manufacturer CO.DON used in the included study cod16HS13 has a valid central European approval. Also, all nationally approved ACI products can only be assigned to the matrix-associated ACI variant [59].

An authorization according to §4b (3) AMG is only required if ATMPs are dispensed to others and the actual power of disposal of the drug changes. In any case, however, a manufacturing permit according to §13 (1) AMG is also always required [57,58].

It is currently unknown whether ATMPs or cell suspensions not requiring a permit are processed for use of the older ACI variants (with a periosteal flap and collagen covered) within a health care facility and applied in an ACI intervention. Several comments on the report plan express the view that both variants are no longer of practical relevance in German health care.

Possible potential of ACI with a periosteal flap and collagen-covered ACI

Based on the results of 2 RCTs each on ACI-P and ACI-C versus standard treatment, no benefit was apparent, nor could a comparable benefit be established with sufficient certainty. Except for a statistically significant beneficial effect (treatment failure) in 1 study in favour of ACI-C, the RCTs showed only numerically inconsistent results for both procedures (see Section 4.7). In contrast, on the basis of the 7 available RCTs, it can be assumed that the M-ACI procedure has a benefit at least comparable to that of standard treatment.

According to several comments on the report plan and preliminary report, M-ACI represents an established therapeutic procedure for large cartilage defects. Since this procedure was determined in this report to have at least comparable benefit to alternative therapies, it will be considered as a component of existing therapeutic options in the assessment of the potential of ACI-C and ACI-P that now follows.

According to the G-BA's rules of procedure: "[...] the potential of a required treatment alternative [...] can arise, for example, if it is associated with the expectation, on the basis of its principle of action and the evidence available to date, that other methods that are more costly, more invasive for the patient or cannot be used successfully in certain patients can be replaced, the method has fewer side effects, it represents an optimization of the treatment or the method can enable more effective treatment in some other way. For assessments according to §137c SGB V, the lack of potential arises in particular when the G-BA positively determines that it is harmful or ineffective on the basis of the available evidence" [60].

When evaluating the potential of the ACI-C and ACI-P procedures, technical advantages of the M-ACI over the older procedures are of crucial importance.

According to the German Society for Orthopaedics and Trauma Surgery (DGOU) [1], M-ACI has the advantage over ACI-P and ACI-C in that it does not require a watertight seal of the membrane or periosteum cover under which the cultured chondrocytes are injected. Removal of periosteum is also not required. In the M-ACI products with current approval or national permit, the chondrocytes are implanted into the defect area in a single step in combination with a carrier matrix. Due to the omission of a membrane cover, M-ACI can in principle also be applied to incompletely demarcated cartilage defect areas. Marlovits 2006 [4] states that this simplifies the surgical procedure and requires a less invasive approach.

Due to the technical advantages of M-ACI noted above, ACI-C and ACI-P are not expected to provide a treatment that is less elaborate or invasive, that can be used more successfully in certain patients, that has fewer side effects, or that provides an optimized and more effective treatment. Therefore, the two ACI procedures do not meet the decisive criteria for the potential of a required treatment method under the G-BA's rules of procedure. This assessment is supported by the fact that, according to comments on the report plan and preliminary report, ACI-C and ACI-P no longer have any relevance in practice in the provision of health care in Germany.

In summary, based on the available results of the total of 14 RCTs, as well as considerations of technical advantages of M-ACI and lack of relevance in practice for ACI-C and ACI-P, no potential of a required treatment alternative can be derived.

6 Conclusion

When all 3 procedures of autologous chondrocyte implantation are considered together (matrix-induced [M-ACI], collagen-covered [ACI-C], with a periosteal flap [ACI-P]), the data provide no hint of benefit or harm versus standard treatment for any of the outcomes. At the medium-term time of analysis (11 to 24 months), heterogeneity between ACI procedures was evident for a large proportion of results, so each was considered separately.

In the 7 studies comparing M-ACI with standard treatments, beneficial effects in favour of M-ACI were shown for the outcomes of function and health-related quality of life. Although the effects do not reach a clinically relevant magnitude, together with a qualitative examination of all other outcomes it can be assumed that M-ACI has a benefit at least comparable to that of current standard treatments.

Within each of the 2 studies comparing ACI-C and ACI-P with standard treatments, 1 study showed a statistically significant effect in favour of ACI-C for 1 outcome (treatment failure). However, no data on the harm of ACI-C are available from the studies, and all other outcomes on both ACI procedures show partly numerically inconsistent results. Therefore, the data

provide no hint of a benefit or harm of ACI-C and ACI-P, and it cannot be estimated with sufficient certainty whether there is a benefit comparable to that of standard treatment.

The results of the 3 studies comparing the ACI procedures in pairs do not contradict the assessment presented above.

References for English extract

Please see full final report for full reference list.

1. Niemeyer P, Albrecht D, Andereya S, Angele P, Ateschrang A, Aurich M et al. Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: a guideline by the working group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Trauma (DGOU). Knee 2016; 23(3): 426-435.

2. Årøen A, Løken S, Heir S, Alvik E, Ekeland A, Granlund OG et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med 2004; 32(1): 211-215.

3. International Cartilage Regeneration & Joint Preservation Society. ICRS Cartilage Injury Evaluation Package [online]. 2000 [Accessed: 27.08.2019]. URL: https://cartilage.org/society/publications/icrs-score.

4. Marlovits S, Zeller P, Singer P, Resinger C, Vécsei V. Cartilage repair: generations of autologous chondrocyte transplantation. Eur J Radiol 2006; 57(1): 24-31.

5. Mistry H, Connock M, Pink J, Shyangdan D, Clar C, Royle P et al. Autologous chondrocyte implantation in the knee: systematic review and economic evaluation. Health Technol Assess 2017; 21(6): 1-294.

6. Dettloff M. Anforderungen an ATMP aus Sicht der GKV [Präsentationsfolien]. 20.09.2018.

7. Marcacci M, Filardo G, Kon E. Treatment of cartilage lesions: what works and why? Injury 2013; 44(Suppl 1): S11-S15.

8. Dozin B, Malpeli M, Cancedda R, Bruzzi P, Calcagno S, Molfetta L et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. Clin J Sport Med 2005; 15(4): 220-226.

9. Lim HC, Bae JH, Song SH, Park YE, Kim SJ. Current treatments of isolated articular cartilage lesions of the knee achieve similar outcomes. Clin Orthop Relat Res 2012; 470(8): 2261-2267.

10. Basad E, Stürz H, Steinmeyer J. Die Behandlung chondraler Defekte mit MACI oder Microfracture: erste Ergebnisse einer vergleichenden klinischen Studie. Orthopädische Praxis 2004; (40): 6-10.

11. Clavé A, Potel JF, Servien E, Neyret P, Dubrana F, Stindel E. Third-generation autologous chondrocyte implantation versus mosaicplasty for knee cartilage injury: 2-year randomized trial. J Orthop Res 2016; 34(4): 658-665.

12. Niemeyer P, Laute V, Zinser W, Becher C, Kolombe T, Fay J et al. A prospective, randomized, open-label, multicenter, phase III noninferiority trial to compare the clinical efficacy of matrix-associated autologous chondrocyte implantation with spheroid technology versus arthroscopic microfracture for cartilage defects of the knee. Orthop J Sports Med 2019; 7(7).

13. Crawford DC, DeBerardino TM, Williams RJ 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. J Bone Joint Surg Am 2012; 94(11): 979-989.

14. Saris D, Price A, Widuchowski W, Bertrand-Marchand M, Caron J, Drogset JO et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. Am J Sports Med 2014; 42(6): 1384-1394.

15. Visña P, Pasa L, Cizmár I, Hart R, Hoch J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques: a randomized controlled study. Acta Chir Belg 2004; 104(6): 709-714.

16. Yoon KH, Yoo JD, Choi CH, Lee J, Lee JY, Kim SG et al. Costal chondrocyte-derived pellet-type autologous chondrocyte implantation versus microfracture for repair of articular cartilage defects: a prospective randomized trial. Cartilage 2020: 1947603520921448.

17. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br 2003; 85(2): 223-230.

18. Fossum V, Hansen AK, Wilsgaard T, Knutsen G. Collagen-covered autologous chondrocyte implantation versus autologous matrix-induced chondrogenesis: a randomized trial comparing 2 methods for repair of cartilage defects of the knee. Orthop J Sports Med 2019; 7(9): 2325967119868212.

19. Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grøntvedt T, Solheim E et al. Autologous chondrocyte implantation compared with microfracture in the knee: a randomized trial. J Bone Joint Surg Am 2004; 86(3): 455-464.

20. Saris DB, Vanlauwe J, Victor J, Haspl M, Bohnsack M, Fortems Y et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. Am J Sports Med 2008; 36(2): 235-246.

21. Bartlett W, Skinner YES, Gooding CR, Carrington RW, Flanagan AM, Briggs TW et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. J Bone Joint Surg Br 2005; 87(5): 640-645.

22. Gooding CR, Bartlett W, Bentley G, Skinner YES, Carrington R, Flanagan A. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: periosteum covered versus type I/III collagen covered. Knee 2006; 13(3): 203-210.

23. Zeifang F, Oberle D, Nierhoff C, Richter W, Moradi B, Schmitt H. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. Am J Sports Med 2010; 38(5): 924-933.

24. Instituto Nacional de Rehabilitación. Arthroscopic autologous chondrocyte implantation versus microfractures: study details [online]. In: ClinicalTrials.gov. 12.04.2017 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01947374.

25. Basad E, Ishaque B, Bachmann G, Sturz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc 2010; 18(4): 519-527.

26. Bentley G, Biant LC, Vijayan S, Macmull S, Skinner YES, Carrington RW. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. J Bone Joint Surg Br 2012; 94(4): 504-509.

27. University Hospital Brest. Comparison of autologous chondrocyte implantation versus mosaicoplasty: a randomized trial (Cartipatch): study details [online]. In: ClinicalTrials.gov. 31.07.2014 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00560664.

28. Hoburg A, Niemeyer P, Laute V, Zinser W, Becher C, Kolombe T et al. Matrix-associated autologous chondrocyte implantation with spheroid technology is superior to arthroscopic microfracture at 36 months regarding activities of daily living and sporting activities after treatment. Cartilage 01.01.2020 [Epub ahead of print].

29. Co.don. Efficacy and safety study of Co.don Chondrosphere to treat cartilage defects: study details [online]. In: ClinicalTrials.gov. 30.07.2019 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01222559.

30. Co.don. Prospective, randomised, open label, multicentre phase-III clinical trial to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product Co.don Chondrosphere (ACT3D-CS) with microfracture in subjects with cartilage defects of the knee with a defect size between 1 and 4 cm^2 [online]. In: EU Clinical Trials Register. [Accessed: 07.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-016466-82.

31. Co.don. Eine prospektive, randomisierte, nicht verblindete, multizentrische klinische Prüfung der Phase III zum Vergleich von Wirksamkeit und Sicherheit des autologen Chondrozytentransplantates co.don chondrosphere (ACT3D-CS) mit der Methode der Mikrofrakturierung bei Knorpeldefekten des Knies mit einer Größe von 1 bis 4 cm^2 [online]. In: Deutsches Register Klinischer Studien. [Accessed: 07.11.2019]. URL: http://www.drks.de/DRKS00004439.

32. Co.don. Prospective, randomised, open label, multicentre phase III clinical trial to compare the efficacy and safety of the treatment with the autologous chondrocyte transplantation product co.don chondrosphere (ACT3D-CS) with mircrofracture in subjects with cartligage defects of the knee with a defect size between 1 und 4 cm^2: study cod16HS13; clinical trial 3-year follow-up report [unpublished]. 2018.

33. Jones HR, Crawford DC. An autologous tissue implant, NeoCart, for treatment of hyaline cartilage injury in the knee. Oper Tech Orthop 2014; 24(4): 264-270.

34. Histogenics. NeoCart phase 2 clinical trial: study details [online]. In: ClinicalTrials.gov. 21.04.2014 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00548119.

35. University Hospital of North Norway. ACI-C versus AMIC: a randomized trial comparing two methods for repair of cartilage defects in the knee: study details [online]. In: ClinicalTrials.gov. 19.02.2019 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01458782.

36. Knutsen G, Drogset JO, Engebretsen L, Grøntvedt T, Isaksen V, Ludvigsen TC et al. A randomized trial comparing autologous chondrocyte implantation with microfracture: findings at five years. J Bone Joint Surg Am 2007; 89(10): 2105-2112.

37. Knutsen G, Drogset JO, Engebretsen L, Grøntvedt T, Ludvigsen TC, Løken S et al. A randomized multicenter trial comparing autologous chondrocyte implantation with microfracture: long-term follow-up at 14 to 15 years. J Bone Joint Surg Am 2016; 98(16): 1332-1339.

38. Dubs L. [Autologous chondrocyte implantation versus microfracturing of the knee joint]. Praxis (Bern 1994) 2004; 93(21): 895-897.

39. Saris D, Price A, Drogset JO, Podškubka A, Tsuchida A, Bezuidenhoudt M et al. SUMMIT prospective, randomized, controlled trial: response rates to matrix-induced autologous chondrocyte implant (MACI) versus microfracture (MFX) by lesion characteristics. Orthop J Sports Med 2013; 1(4 Suppl 1).

40. Vericel. Superiority of MACI versus microfracture treatment in patients with symptomatic articular cartilage defects in the knee (SUMMIT): study details [online]. In: ClinicalTrials.gov. 25.10.2019 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00719576.

41. Genzyme Europe. A prospective, randomized, open-label, parallel-group, multicenter study to demonstrate the superiority of matrix-induced autologous chondrocyte implantation (MACI implant) versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea [online]. In: EU Clinical Trials Register. [Accessed: 07.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-004817-16.

42. Vericel. Superiority of MACI versus microfracture treatment in patients with symptomatic articular cartilage defects in the knee (SUMMIT): study results [online]. In: ClinicalTrials.gov. 25.10.2019 [Accessed: 07.11.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00719576.

43. Genzyme Europe. A prospective, randomized, open-label, parallel-group, multicenter study to demonstrate the superiority of matrix-induced autologous chondrocyte implantation (MACI implant) versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea: clinical study report; synopsis [online]. In: EU Clinical Trials Register. 29.08.2012 [Accessed: 22.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2006-004817-16/1/14990.

44. Brittberg M, Recker D, Ilgenfritz J, Saris DBF. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: five-year follow-up of a prospective randomized trial. Am J Sports Med 2018; 46(6): 1343-1351.

45. Vericel. Extension study for participants of MACI00206 study of MACI for the treatment of symptomatic articular cartilage defects of the knee (extension): study details [online]. In: ClinicalTrials.gov. 25.10.2019 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT01251588.

46. Genzyme Europe. An extension protocol for participants of genzyme-sponsored prospective, randomized, open-label, parallel-group, multicenter study of matrix-induced autologous chondrocyte implantation (MACI implant) for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea [online]. In: EU Clinical Trials Register. [Accessed: 07.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-016970-33.

47. Vericel. Extension study for participants of MACI00206 study of MACI for the treatment of symptomatic articular cartilage defects of the knee (extension): study results [online]. In: ClinicalTrials.gov. 25.10.2019 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/ct2/show/results/NCT01251588.

48. Genzyme Europe. An extension protocol for participants of genzyme-sponsored prospective, randomized, open-label, parallel-group, multicenter study of matrix-induced autologous chondrocyte implantation (MACI implant) for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea: clinical trial results [online]. In: EU Clinical Trials Register. 04.10.2019 [Accessed: 07.11.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-016970-33/results.

49. Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. Am J Sports Med 2009; 37(Suppl 1): 10S-19S.

50. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med 2011; 39(12): 2566-2574.

51. Van Assche D, Staes F, Van Caspel D, Vanlauwe J, Bellemans J, Saris DB et al. Autologous chondrocyte implantation versus microfracture for knee cartilage injury: a prospective randomized trial, with 2-year follow-up. Knee Surg Sports Traumatol Arthrosc 2010; 18(4): 486-495.

52. TiGenix. RCT of ChondroCelect (in an ACI procedure) vs microfracture in the repair of cartilage defects of the knee (TIGACT01): study details [online]. In: ClinicalTrials.gov. 26.09.2011 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT00414700.

53. TiGenix. RCT of ChondroCelect (in an ACI procedure) vs microfracture in the repair of cartilage defects of the knee (TIGACT01): study results [online]. In: ClinicalTrials.gov. 26.09.2011 [Accessed: 07.11.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00414700.

54. MCTTBio. A multi-center, active-controlled, open-label, phase II trial to compare the efficacy and safety for treatment of autologous chondrocytes implantation with CartiLife versus microfracture for patient with chondral defects in the knee [online]. In: Clinical Research Information Service 06.07.2015 [Accessed: 07.11.2019]. URL: http://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=3780.

55. Biosolution. Study to assess the efficacy and safety of treatment of articular cartilage lesions with CartiLife: study details [online]. In: ClinicalTrials.gov. 04.06.2018 [Accessed: 07.11.2019]. URL: https://ClinicalTrials.gov/show/NCT03545269.

56. Europäisches Parlament, Rat der Europäischen Union. Verordnung (EG) Nr. 1394/2007 des Europäischen Parlaments und des Rates vom 13. November 2007 über Arzneimittel für neuartige Therapien und zur Änderung der Richtlinie 2001/83/EG und der Verordnung (EG) Nr. 726/2004. Amtsblatt der Europäischen Union 2007; 50(L324): 121-137.

57. Paul-Ehrlich-Institut. Arzneimittel für neuartige Therapien: regulatorische Anforderungen und praktische Hinweise [online]. 06.2012 [Accessed: 06.05.2020]. URL: https://www.pei.de/SharedDocs/Downloads/DE/regulation/beratung/innovationsbuero/broschuere-atmp.pdf?__blob=publicationFile&v=4.

58. Bundesministerium der Justiz und für Verbraucherschutz. Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG) [online]. 22.03.2020 [Accessed: 15.05.2020]. URL: http://www.gesetze-im-internet.de/amg_1976/BJNR024480976.html

59. Paul-Ehrlich-Institut. Biotechnologisch bearbeitete Gewebeprodukte [online]. 23.03.2020 [Accessed: 06.04.2020]. URL: https://www.pei.de/DE/arzneimittel/atmp/tep/tep-node.html.

60. Gemeinsamer Bundesausschuss. Verfahrensordnung des Gemeinsamen Bundesausschusses [online]. URL: https://www.g-ba.de/informationen/richtlinien/42/.

61. Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

62. Lefebvre C, Manheimer E, Glanville J. Searching for studies [online]. In: Higgings JPT, Green S (Ed). Cochrane handbook for systematic reviews of interventions: version 5.1.0. 03.2011 [Accessed: 05.09.2018]. URL: http://handbook-5-1.cochrane.org/chapter_6/6_searching_for_studies.htm.

The full report (German version) is published under

https://www.iqwig.de/projekte/n19-02.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

A1.1.1 Systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to July 08, 2019

The following filter was adopted:

- Systematic review: Wong [61] – High specificity strategy

#	Searches
1	chondrocytes/tr
2	tissue engineering/ and cartilage*.hw.
3	((chondro* or cartilage*) adj3 (implantation* or transplantation*)).ti,ab.
4	maci.ti,ab.
5	or/1-4
6	cochrane database of systematic reviews.jn.
7	(search or medline or systematic review).tw.
8	meta analysis.pt.
9	or/6-8
10	9 not (exp animals/ not humans.sh.)
11	and/5,10
12	11 and (english or german).lg.
13	..l/ 12 yr=2014-Current

2. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews Issue 7 of 12, July 2019

ID	Search
#1	[mh ^chondrocytes/tr]
#2	[mh ^"tissue engineering"] and cartilage*:kw
#3	((chondro* or cartilage*) near/3 (implantation* or transplantation*)):ti,ab
#4	maci:ti,ab
#5	#1 or #2 or #3 or #4
#6	#5 with Cochrane Library publication date from Jan 2014 to present, in Cochrane Reviews, Cochrane Protocols

A1.1.2 Primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to September Week 1 2019
- Ovid MEDLINE(R) Daily Update September 16, 2019

The following filter was adopted:

- RCT: Lefebvre [62] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	chondrocytes/tr
2	tissue engineering/ and cartilage*.hw.
3	((chondro* or cartilage*) adj3 (implantation* or transplantation*)).ti,ab.
4	maci.ti,ab.
5	or/1-4
6	randomized controlled trial.pt.
7	controlled clinical trial.pt.
8	(randomized or placebo or randomly or trial or groups).ab.
9	drug therapy.fs.
10	or/6-9
11	10 not (exp animals/ not humans.sh.)
12	and/5,11
13	12 not (comment or editorial).pt.
14	13 and (english or german).lg.

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to September 17, 2019
- Ovid MEDLINE(R) Epub Ahead of Print September 17, 2019

#	**Searches**
1	((chondro* or cartilage*) and (implantation* or transplantation*)).ti,ab.
2	maci.ti,ab.
3	or/1-2
4	(clinical trial* or random* or placebo).ti,ab.
5	trial.ti.
6	or/4-5
7	and/3,6

#	Searches
8	7 not (comment or editorial).pt.
9	8 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 September 18

The following filter was adopted:

- RCT: Wong [61] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	(chondrocyte* or cartilage*).hw.
2	(implant* or transplantation* or autotransplantation*).hw. or tissue scaffold/
3	and/1-2
4	((chondro* or cartilage*) adj3 (implantation* or transplantation*)).ti,ab.
5	maci.ti,ab.
6	or/3-5
7	(random* or double-blind*).tw.
8	placebo*.mp.
9	or/7-8
10	and/6,9
11	10 not medline.cr.
12	11 not (exp animal/ not exp human/)
13	12 not (conference abstract or conference review or editorial).pt.
14	13 and (english or german).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 9 of 12, September 2019

ID	Search
#1	[mh ^chondrocytes/tr]
#2	[mh ^"tissue engineering"] and cartilage*:kw
#3	((chondro* or cartilage*) near/3 (implantation* or transplantation*)):ti,ab
#4	maci:ti,ab
#5	#1 or #2 or #3 or #4
#6	#5 in Trials

A.2 – Searches in study registries

1. **ClinicalTrials.gov**

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
cartilage implantation OR cartilage implant OR cartilage transplantation OR chondrocyte implantation OR chondrocyte implant OR chondrocyte transplantation OR MACI

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
((chondro* OR cartilage*) AND (implant* OR transplant*)) OR MACI

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
cartilage injuries OR cartilage defect* OR cartilage lesion* OR articular cartilage OR knee AND defect* OR knees AND defect* OR chondrocytes