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Austrian Institute for
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Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

AAOS .....American Academy of Orthopaedic Surgeons
ACI.....Autologous Chondrocyte Implantation
ADL .....Activities of Daily Living
AMIC .....Autologous Matrix-Induced Chondrogenesis
AMIC+ .....Autologous Matrix-Induced Chondrogenesis with BMAC
AIHTA .....Austrian Institute for Health Technology Assessment
ATMP.....Advanced Therapy Medicinal Products
BMAC .....Bone Marrow Aspirate Concentrate
BMI .....Body Mass Index
CE.....Conformité Européenne (European Conformity)
CG .....Control Group
CI.....Confidence Interval
CROM.....Clinician-Reported Outcome Measure
ECM.....Extracellular Matrix
EUnetHTA ...European Network for Health Technology Assessment
FU .....Follow-up
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
HA.....Hyaluronic Acid
HTA .....Health Technology Assessment
HRQoL .....Health-related Quality of Life
ICRS.....International Cartilage Regeneration & Joint Preservation Society
IG.....Intervention Group
IKDC.....International Knee Documentation Committee
IQR.....Interquartile Range
KOOS.....Knee Injury and Osteoarthritis Outcome Score
LBI-HTA .....Ludwig Boltzmann Institute for Health Technology Assessment
MACI .....Matrix-Assisted Chondrocyte Implantation
MCID.....Minimal Clinically Important Difference
mCKRS.....Modified Cincinnati Knee Rating System
MD .....Mean Difference
MFx.....Microfracture
MOCART .....Magnetic Resonance Observation of Cartilage Repair Tissue
MRI.....Magnetic Resonance Imaging
MSC .....Mesenchymal Stem Cells
NA.....Not Applicable
NSAID .....Nonsteroidal Anti-Inflammatory Drug
NICE.....National Institute for Health and Care Excellence
NR.....Not Reported
NRCT.....Non-Randomised Controlled Trial
NS.....Not Significant
OA .....Osteoarthritis
OCD.....Osteochondritis Dissecans
OIS .....Optimal Information Size
PICO .....Population, Intervention, Comparison, Outcome
PROM.....Patient-Reported Outcome Measure
QoL .....Quality of Life
RCT.....Randomised Controlled Trial
RoB.....Risk of Bias
ROBIS.....Risk Of Bias In Systematic Reviews
ROBINS-I.....Risk Of Bias In Non-randomised Studies of Interventions
SD.....Standard Deviation
SF-36.....Short Form 36 Health Survey
SR.....Systematic Review
SoC.....Standard of Care
TAS .....Tegner Activity Scale
VAS .....Visual Analogue Scale
WOMAC.....Western Ontario and McMaster Universities Osteoarthritis Index

Executive Summary

Introduction

Health Problem

cartilage is a connective tissue in the knee joint

Cartilage is a specialised connective tissue composed of two main components: the extracellular matrix (ECM) and the chondrocytes, responsible for the knee joint's homeostasis.

defects occur due to senescence, abnormal forces, local diseases, systemic factors

categorised in 5 grades: normal (0) up to severely abnormal (IV)

It is evident that in addition to senescence (age-related cellular changes), abnormal forces (traumatic injuries, repetitive microtrauma, overloading), local diseases (osteochondritis dissecans, degenerative diseases) or systemic risk factors (age, genetic abnormalities, predispositions, body mass index, etc.) can prevent joint homeostasis and, therefore, the maintenance and restoration of matrix molecules, which in turn stimulates a vicious cycle of matrix degradation and inflammation of the synovium, resulting in continuous degeneration. Cartilage is categorised into five grades, from normal (Grade 0) to severely abnormal (Grade IV) by the International Cartilage Regeneration & Joint Preservation Society. In particular, defects of Grade II (<50% of cartilage depth) and III (>50% of cartilage depth and calcified layer) are diagnosed, characterised by swelling, pain dysfunction, and a consequent decrease in quality of life (QoL).

limited regenerative capacity necessitates external support

Cartilage has a limited regenerative capacity due to its avascular nature, which necessitates supporting cartilage regeneration. There are no specific data on cartilage repair in Austria, but 74,815 general knee joint operations were performed in 2023, and older data show cartilage or (osteo)chondral lesions in 61 to 63% of knee arthroscopies.

Description of Technology

AMIC

one-stage matrix-assisted cartilage repair (AMIC) in combination with microfracture (MFx)

One-stage matrix-assisted cartilage repair (AMIC- autologous matrix-induced chondrogenesis) combines microfracture with matrix or scaffold placement to cover cartilage defects. The scaffold, made from biomaterials like collagen or hyaluronan, captures cells migrating from the subchondral layer. The matrix, which decomposes over time, provides stability and may promote cell differentiation and cartilage regeneration.

AMIC+

augmentation with bone marrow aspirate concentrate (BMAC) = AMIC+

AMIC can be enhanced with cell suspensions such as bone marrow aspirate concentrate (BMAC). It is harvested from the iliac crest and processed through centrifugation to concentrate cells and growth factors. Despite low stem cell concentration, its potential therapeutic benefits come from growth factors and anti-inflammatory properties.

Methods

This report aimed to analyse whether AMIC and AMIC+ are as safe and more effective than standard therapy in adults with indications for cartilage replacement knee surgery. A systematic literature search in four databases and an additional hand search were performed to identify RCTs and NRCTs (for AMIC+ only) that met the predefined eligibility criteria, resulting in a total of 988 hits with manufacturers' submissions. Two researchers independently performed study selection, data extraction and quality assessment of the included studies. The certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme. The results were mainly synthesised narratively, with a random-effects meta-analysis carried out if sufficient data were available.

aim:
effectiveness +
safety of AMIC and AMIC+

systematic search in
4 databases,
quality appraisal

GRADE

Domain effectiveness

The following effectiveness outcomes were considered critical to derive a recommendation: Physical function, activity level, health-related quality of life (HRQoL), pain, necessity of joint replacement, structural repair.

effectiveness outcomes:
quality of life, pain,
necessity of joint
replacement,
structural repair

Domain safety

Serious adverse events and adverse events were considered critical safety outcomes for decision-making.

safety outcomes:
(serious) adverse events

Results

This review included 10 studies (13 publications) with 786 total patients (697 in 8 RCTs, 89 in 2 NRCTs) with osteochondral defects. For standard AMIC, seven RCTs were analysed (including three from a previous LBI-HTA-report), comparing AMIC to either microfracture (MFx, one-stage procedure) or (matrix-induced) autologous chondrocyte implantation (ACI/MACI, two-stage procedures). AMIC+ was evaluated in one RCT and two NRCTs. Certainty of evidence varied: low to moderate certainty for AMIC versus MFx (one-stage) but very low certainty for AMIC versus ACI (two-stage) and all AMIC+ comparisons. Most studies showed an increased risk of bias in both patient-reported and clinician-reported outcomes.

8 randomised controlled
trials (RCTs) for
697 patients (pts),
2 non-randomised
controlled trials (NRCTs)
for 89 pts

certainty of evidence
very low to moderate

AMIC

Seven studies with a total of 673 patients evaluated AMIC versus standard of care. Six studies compared AMIC with MFx (n=632), and one study with ACI (n=41). Primary endpoints were clinical evaluations through patient-reported scores such as the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Visual Analogue Scale (VAS), as well as magnetic resonance imaging (MRI) evaluation.

6 RCTs on AMIC versus (vs.)
MFx, 1 RCT on AMIC vs.
autologous chon-drocyte
implantation (ACI)

Effectiveness

Considering AMIC versus MFx, KOOS pain showed no significant differences at 24 months across studies. VAS pain scores showed no significant difference (-2.27; 95%CI: -7.42 to 2.89). Structural repair demonstrated significant improvement in defect filling for AMIC in three studies (e.g. (85.5% vs. 30.9% achieving ≥75% filling, $p<0.0001$). Function scores, like the KOOS total scores, varied between studies, with one showing significant improvement for AMIC (22.5 points, $p<0.0001$), while others found no difference.

AMIC vs. MFx:
no stat. significant
differences in pain,
some studies showing
stat. significant differences
in QoL, structural repair
and function

International Knee Documentation Committee (IKDC) scores showed inconsistent results with high heterogeneity (pooled difference: 7.06, 95%CI: -3.90 to 18.03, I^2=91.2%). In light of HRQoL, KOOS QoL was reported in three studies comparing AMIC with MFx, with one showing significant improvement for AMIC (73.9 vs. 48.8 with a posterior probability of superiority of 1.00, exceeding the prespecified Bayesian posterior probability). The Short Form Health Survey (SF-36) showed no significant differences between groups at 12 months.

Regarding AMIC versus ACI, no significant differences in KOOS pain and VAS were detected at 24 months. Structural repair was not reported. Function scores, like KOOS total and Lysholm score, did not demonstrate a significant difference between study groups either. HRQoL was not assessed in the included study.

no stat. significant differences between AMIC and ACI

Safety

Regarding safety, serious adverse events occurred in 0-15.6% of AMIC patients versus 0-20.2% in MFx patients. Re-operation rates were generally lower in AMIC groups. Adverse events mostly ranged from 0% to 60% in the IG and 0% to 77% in the MFx group at 24 months.

serious adverse events (SAE) 0-15.6% AMIC vs. 0-20.2% MFx

Comparing AMIC with ACI, no serious adverse events were reported, and comparable re-operation rates between groups (14.3% versus 15.0% for re-arthroscopy 4.8% vs. 5.0% for re-operations) were found. Adverse events were not reported.

no SAEs reported in AMIC vs. ACI

AMIC+

One RCT and two NRCTs compared AMIC+ with different comparators: AMIC (RCT, n=24), MACI (NRCT, n=89), and MFx (NRCT, n=52). Primary endpoints included patient-reported measures like VAS, Lysholm score, IKDC objective/subjective, and Tegner Activity Score (TAS), along with radiographs and MRI evaluations.

AMIC+ vs. AMIC (1 RCT), MACI (1 NRCT) + MFx (1 NRCT)

Effectiveness

For AMIC+ versus AMIC, no statistically significant differences were found in any endpoints at any time, including patient-reported outcomes of morbidity (KOOS pain, VAS), function (KOOS subscale, TAS, Lysholm Score), HRQoL, and clinician-reported outcomes of structural repair (MRI, defect size and filling) and function (IKDC objective).

no stat. significant difference between AMIC+ and AMIC

AMIC+ versus MACI showed similar outcomes in most measures, except for IKDC subjective at final follow-up (~60 months), where AMIC+ demonstrated better knee function (82.52 ±10.72 vs. 75.70 ±9.85, p=0.015). No significant differences were found in other measures at final follow-up, namely KOOS subscales, VAS, Lysholm, defect filling, complete integration and IKDC objective. Group differences were not analysed at 24 months follow-up.

no stat. significant difference between AMIC+ and MACI, except for IKDC subjective

AMIC+ versus MFx showed significant advantages for AMIC+ at 60 months in KOOS pain (95 [10] vs. 87 [31], p=0.023), KOOS Sport and recreation (6 [1.5] vs. 4 [2], p<0.001), and IKDC objective (p<0.001). KOOS ADL and QoL, TAS, Lysholm Score and IKDC subjective did not show statistical significance.

no stat. significant difference between AMIC+ and MFx regarding morbidity and function

Safety

Regarding patient safety, one adverse event was observed in the intervention group of AMIC+ versus AMIC.

No adverse reactions or postoperative infections were noted in any of the patients in the AMIC+ versus MACI study, while both groups showed one case of debridement and mobilisation.

In the comparison of AMIC+ versus MFx, one adverse event occurred in the intervention group.

not stat. significant difference between AMIC+ and standard therapies regarding safety

Ongoing studies

Five ongoing RCTs evaluate single-step scaffold procedures: four compare AMIC to matrix-assisted autologous chondrocyte transplantation (n=80), MFx (n=185), engineered cartilage graft (n=150), and modified MFx (n=100), while one studies AMIC+ versus MFx (n=200). Completion dates range from 2025-2032, with primary endpoints focusing on patient-reported function and pain outcomes.

5 ongoing RCTs (4 AMIC; 1 AMIC+)

Discussion

The review evaluated AMIC and AMIC+ compared to standard procedures (MFx and two stage repairs). Internal validity concerns arose from lack of blinding and high dropout rates in several trials, with some RCTs showing an increased risk of bias for patient-reported outcomes. Key evidence gaps include uncertainties about long-term effectiveness (most studies limited to 24 months), optimal defect characteristics for treatment selection, and variation in scaffold materials preventing conclusions about optimal materials. For AMIC versus MFx, recent evidence suggests some superiority in structural repair and function, contrasting with previous findings. However, the evidence for AMIC versus ACI remains limited (one small trial). For AMIC+, evidence is particularly sparse with only three studies (one RCT, two NRCTs) showing very low certainty across all endpoints.

increased risk of bias due to lack of blinding

uncertainties about long-term effectiveness

possible superiority for AMIC over MFx, limited evidence for other comparisons

While other studies consider single-step scaffold insertion a beneficial intermediate treatment option between microfracture and complex cell-based therapies, the field would benefit from standardisation in outcome reporting and focused research on specific comparisons (AMIC+ versus AMIC if standard AMIC is approved, or comparing to current treatment standards in contexts where AMIC is not yet approved).

need for standardisation in outcome reporting

Conclusion

Low to moderate certainty of evidence suggests AMIC to be more effective than microfracture for structural repair, with comparable or better results for other outcomes. However, currently available trial results limit a conclusion on long-term data beyond 24 months and optimal patient selection (regarding defect characteristics). Evidence for AMIC versus ACI is based on a single small study while AMIC+ data is limited to three small studies with mixed results.

low to moderate certainty of evidence for superiority of AMIC compared to MFx, very low certainty of evidence for AMIC+

A re-evaluation for AMIC is recommended for 2033. For AMIC+, a review is recommended for 2028 following the publication of results from the ongoing study, otherwise also for 2033.

re-evaluation recommended in 2033 (AMIC), or in 2028 (AMIC+)

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Knorpel als spezialisiertes Bindegewebe

Knorpel ist spezialisiertes Bindegewebe, das aus zwei Hauptkomponenten besteht: der extrazellulären Matrix (EZM) und den Chondrozyten, die für die Homöostase des Kniegelenks verantwortlich sind.

Defektentstehung: Seneszenz, abnormale Kräfte, lokale Erkrankungen, systemische Risikofaktoren

Neben der Seneszenz (altersbedingte zelluläre Veränderungen) können auch abnormale Kräfte, lokale Erkrankungen und systemische Risikofaktoren die Gelenkhomöostase beeinträchtigen. Dies stört die Aufrechterhaltung und Regeneration der Matrixmoleküle und löst einen sich selbst verstärkenden Kreislauf aus: Der Abbau der Matrix und die Entzündung der Synovialmembran (Gelenkinnenhaut) führen zu einer fortschreitenden Degeneration.

im Detail: Traumata, Überbelastung, Alter, Genetik, Prädispositionen, Osteochondritis dissecans, degenerative Erkrankungen

Als abnormale Kräfte werden traumatische Knieverletzungen, chronische repetitive Mikrotraumata oder (Über-)Belastungen verstanden. Meistens sind sie sportbedingt, können aber auch bei Alltagsaktivitäten auftreten. Systemische Risikofaktoren beinhalten Alter, genetische Anomalien und Prädisposition für frühzeitige Verschlechterung, Body Mass Index (BMI) und erworbene metabolische Faktoren, wobei das Alter eine entscheidende Rolle bei der Entwicklung von (osteo)chondralen Defekten und der Indikation für Knorpelreparatur spielt. Zu den lokalen Erkrankungen zählen insbesondere Osteochondritis dissecans (OCD) und degenerative Erkrankungen, die durch fortschreitende Gewebszerstörung gekennzeichnet sind. Der Krankheitsprozess der OCD beginnt tief unter der Gelenkoberfläche und löst die Entwicklung von Gelenkkörpern innerhalb der Gelenkmatrix aus.

kategorisiert in 5 Grade von gesundem Knorpel (0) bis vollständiger Knorpelschaden (IV)

Die International Cartilage Regeneration & Joint Preservation Society (ICRS) kategorisiert Knorpel in fünf Grade von gesundem Knorpel (Grad 0) bis zum vollständigen Knorpelschaden (Grad IV). Insbesondere werden Defekte von Grad II (<50 % der Knorpeltiefe) und III (>50 % der Knorpeltiefe und kalzifizierte Schicht) diagnostiziert.

Folgen: Schwellungen, Schmerzen, verminderte Lebensqualität, Arthrose, Arbeitsunfähigkeit

Unabhängig von der Defektursache erleben die meisten Patient:innen Schwellungen, Schmerzfunktionsstörungen und eine daraus resultierende Verminderung der Lebensqualität. Unbehandelte Knorpeldefekte können zu frühzeitiger Arthrose führen, die durch fortschreitende Schmerzen und funktionelle Beeinträchtigung gekennzeichnet ist. Die daraus resultierende Arbeitsunfähigkeit betrifft überwiegend Personen im produktiven Alter und könnte mit zusätzlichen gesellschaftlichen Kosten verbunden sein.

Regenerationsfähigkeit ist begrenzt und macht chirurgische Unterstützung erforderlich

Da Knorpelgewebe nicht durchblutet (avaskulär) ist, kann es sich nur begrenzt selbst regenerieren. Nach Verletzungen oder bei Verschleiß benötigt der Knorpel daher (chirurgische) Unterstützung. Chirurgische Eingriffe zur Knorpelreparatur und -regeneration werden je nach Art des Schadens durchgeführt – entweder bei reinen Knorpeldefekten oder bei osteochondralen Defekten, bei denen auch der darunter liegende Knochen geschädigt ist.

Standardtherapien: einzeitig und zweizeitig

Derzeitige Standardtherapien zur Knorpelreparatur sind einzeitige Verfahren, wie Mikrofrakturierung (MFx) und Mosaikplastik, oder zweizeitige Verfahren, wie die (matrix-induzierte) autologe Chondrozytenimplantation (ACI/MACI).

Es sind keine spezifischen Daten zur Knorpelreparatur in Österreich veröffentlicht. Allerdings wurden in Österreich 74.815 allgemeine Kniegelenkoperationen im Jahr 2023 durchgeführt, und ältere Daten zeigen Knorpel- oder (osteo)chondrale Läsionen in 61 bis 63 % der Knieарthroskopien.

fehlende Daten zur Knorpelreparatur in Ö
61-63 % ermittelte Defekte bei Knie-Arthroskopien

Beschreibung der Technologie

Einzeitiger matrix-assistierter Knorpelersatz im Knie (AMIC)

Der einzeitige matrix-assistierte Knorpelersatz, kombiniert die Mikrofrakturierung mit einer Matrix, die als struktureller Platzhalter für die Defektabdeckung während eines chirurgischen Eingriffs dient. Für dieses Verfahren existieren verschiedene Bezeichnungen, beispielsweise matrix-augmentierte Knochenmarkstimulation und Autologe Matrixinduzierte Chondrogenese (AMIC, Geistlich Söhne AG; Schweiz). Letztere, ein geschützter Begriff, ist am geläufigsten und wird deshalb in diesem Bericht verwendet. Die Kollagenmatrix fängt migrierende Zellen auf und bietet Stabilität zur Knorpelregeneration. Die zellfreien (temporären) Platzhalter sind als feste Materialien oder injizierbare Gele verfügbar und können je nach Verfahren durch Naht oder Klebung fixiert werden.

einzeitige Behandlung mit Matrix (AMIC – Autologe Matrixinduzierte Chondrogenese) kombiniert mit Mikrofrakturierung (MFx)

AMIC mit Knochenmarkaspiratkonzentrat (AMIC+)

Bei einem AMIC+-Eingriff wird die Kollagen-Matrix mit Knochenmarkaspiratkonzentrat (BMAC) angereichert. Das BMAC wird während derselben Operation aus dem Beckenkamm entnommen und durch Zentrifugation aufbereitet. Obwohl es nur eine geringe Menge an mesenchymalen Stammzellen enthält, kann das BMAC durch seine Wachstumsfaktoren und entzündungshemmenden Eigenschaften therapeutische Vorteile für die Knorpelregeneration bieten.

AMIC mit Knochenmarkaspiratkonzentrat (BMAC)=AMIC+

Methoden

Das Ziel dieser Bewertung war es zu analysieren, ob AMIC und AMIC+ bei Erwachsenen mit Indikationen für eine Knorpelersatz-Operation am Knie genauso sicher sowie wirksamer sind als die Standardtherapien.

Ziel:
Wirksamkeit + Sicherheit von AMIC und AMIC+

Eine systematische Literatursuche in vier Datenbanken sowie eine zusätzliche manuelle Handsuche wurden durchgeführt, um randomisierte kontrollierte Studien (RCTs) und nicht-randomisierte kontrollierte Studien NRCTs (NRCTs, nur für AMIC+) zu identifizieren, die den vordefinierten Einschlusskriterien entsprachen. Dies führte zu insgesamt 988 Treffern einschließlich Herstellereinreichungen. Zusätzlich wurden Studien aus einem früheren Bericht des Ludwig-Boltzmann-Instituts für Health Technology Assessment (LBI-HTA) aus 2019 zum Knorpelersatz berücksichtigt. Zwei Forscher:innen führten unabhängig voneinander die Studienauswahl, Datenextraktion und Qualitätsbewertung der eingeschlossenen Studien durch. Die interne Validität der eingeschlossenen Studien wurde mittels des Cochrane Risk of Bias Tools v2 für RCTs und ROBINS-I für NRCTs bewertet. Die Vertrauenswürdigkeit der Evidenz wurde anhand des GRADE-Schemas (Grading of Recommendations Assessment, Development and Evaluation) beurteilt. Die Ergebnisse wurden hauptsächlich narrativ zusammengefasst, wobei eine Random-Effects-Metaanalyse durchgeführt wurde, wenn ausreichend Daten verfügbar waren.

systematische Literatursuche in 4 Datenbanken

Qualitätsbewertung:
RoB V2; ROBINS-I

GRADE

Klinische Wirksamkeit

Die folgenden Ergebnisse zur Wirksamkeit wurden als entscheidungsrelevant definiert:

- Körperliche Funktion, Aktivitätsniveau
- Gesundheitsbezogene Lebensqualität
- Schmerzen
- Notwendigkeit eines Gelenkersatzes
- Strukturelle Wiederherstellung

Endpunkte zur Wirksamkeit: Funktion, Lebensqualität, Schmerzen, Gelenkersatz, strukturelle Wiederherstellung

Sicherheit

Die folgenden Ergebnisse zur Sicherheit wurden als entscheidungsrelevant definiert:

- Unerwünschte Ereignisse
- Schwere unerwünschte Ereignisse

Endpunkte zur Sicherheit: (schwere) unerwünschte Ereignisse (SUE/UE)

Ergebnisse

Es wurden zehn Studien (13 Publikationen, einschließlich drei Studien aus einem früheren LBI-HTA-Bericht) mit insgesamt 786 Patient:innen (697 in 8 RCTs), 89 in 2 NRCTs) mit osteochondralen Defekten eingeschlossen, die AMIC entweder mit MFx oder ACI/MACI verglichen. AMIC+ wurde in einem RCT und zwei NRCTs evaluiert. Die Vertrauenswürdigkeit der Evidenz variierte: niedrige bis moderate Evidenz für AMIC versus MFx, sehr niedrige Evidenz für AMIC versus ACI und alle AMIC+ Vergleiche. Die meisten Studien zeigten ein erhöhtes Verzerrungsrisiko bei Endpunkten, welche sowohl von Patient:innen als auch von Kliniker:innen berichtet wurden.

10 Studien: 8 randomisiert kontrollierte Studien (RCTs) und 2 nicht randomisiert kontrollierte Studien (NRCTs)

AMIC

Sieben Studien mit insgesamt 673 Patient:innen bewerteten AMIC im Vergleich zu Standardbehandlung. Sechs Studien verglichen AMIC mit MFx (n=632) und eine Studie mit ACI (n=41). Die primären Endpunkte waren klinische Bewertungen durch patient:innen-berichtete Scores wie den Knee Injury and Osteoarthritis Outcome Score (KOOS) und die Visual Analogue Scale (VAS), sowie die Beurteilung mittels Magnetresonanztomographie (MRT).

6 Studien zu AMIC vs. MFx
1 Studie zu AMIC vs. Autologer Chondrozytenimplantation (ACI)

Klinische Wirksamkeit

Beim Vergleich zwischen AMIC und MFx zeigte die Schmerzsubskala des KOOS keine signifikanten Unterschiede nach 24 Monaten in den Studien. Auch die VAS-Werte zeigten keinen signifikanten Unterschied (-2,27; 95 % KI: -7,42 bis 2,89). Die strukturelle Wiederherstellung demonstrierte eine signifikante Verbesserung der Defektfüllung für AMIC in drei Studien (z. B. 85,5 % vs. 30,9 % erreichten ≥75 % Füllung, $p<0{,}0001$). Funktionsscores wie der KOOS-Gesamtscore variierten zwischen den Studien, wobei eine Studie eine signifikante Verbesserung für AMIC zeigte (Mittelwertdifferenz von 22,5 Punkten, $p<0{,}0001$), während andere keinen Unterschied fanden. Der International Knee Documentation Committee (IKDC) Score zeigte uneinheitliche Ergebnisse mit hoher Heterogenität (gepoolte Mittelwertdifferenz: 7,06, 95 % KI: -3,90 bis 18,03, $I^2=91{,}2$ %). Bezüglich gesundheitsbezogener Lebensqualität wurde KOOS QoL in drei Studien berichtet, die AMIC mit MFx verglichen, von denen eine Studie eine signifikant bessere Lebensqualität für

AMIC vs. MFx: keine stat. signifikanten Unterschiede bei Schmerzen; stat. signifikante Unterschiede in der strukturellen Wiederherstellung und Lebensqualität zugunsten AMIC nach 24 Monaten

Teilnehmende der AMIC-Gruppe zeigte (73,9 vs. 48,8 mit einer A-posteriori Wahrscheinlichkeit von 1,00, die die vorab festgelegte Bayes'sche A-posteriori Wahrscheinlichkeit überschritt). Der Short Form Health Survey (SF-36) zeigte keine signifikanten Unterschiede zwischen den Gruppen nach 12 Monaten.

keine stat. signifikanten Unterschiede zwischen AMIC und ACI

Bezüglich AMIC versus ACI wurden keine signifikanten Unterschiede bei der KOOS Schmerz-Skala und der VAS nach 24 Monaten festgestellt. Die strukturelle Reparatur wurde nicht berichtet. Funktionsscores wie KOOS-Gesamtscore und Lysholm-Score zeigten ebenfalls keinen signifikanten Unterschied zwischen den Studiengruppen. Die Lebensqualität wurde in der eingeschlossenen Studie nicht bewertet.

Sicherheit

AMIC vs. MFx:
SUE: 0-15,6 % vs. 0-20,3 %

UE: 0-60 % vs. 0-77 %

Bezüglich der Sicherheit traten schwere unerwünschte Ereignisse bei 0-15,6 % der AMIC-Patient:innen gegenüber 0-20,2 % bei MFx-Patient:innen auf. Die Re-Operationsraten waren in den AMIC-Gruppen generell niedriger. Unerwünschte Ereignisse reichten von 0 % bis 60 % in der Interventionsgruppe und 0 % bis 77 % in der MFx-Gruppe nach 24 Monaten.

AMIC vs. ACI:
keine SUE in beiden Gruppen

Beim Vergleich zwischen AMIC und ACI wurden keine schweren unerwünschten Ereignisse berichtet und vergleichbare Re-Operationsraten zwischen den Gruppen (14,3 % gegenüber 15,0 % für Re-Arthroskopie, 4,8 % gegenüber 5,0 % für Re-Operationen) festgestellt. Unerwünschte Ereignisse wurden nicht berichtet.

AMIC+

AMIC+ vs. AMIC (1 RCT), MACI (1 NRCT) + MFx (1 NRCT)

In einem RCT sowie zwei NRCTs wurde AMIC+ mit der Standardbehandlung verglichen. Komparatoren stellten AMIC (RCT; n=24), MACI (1 NRCT; n=37) und MFx (n=52) dar. Als primäre Endpunkte für die klinische Bewertung dienten die Patient:innen-berichteten Ergebnismaße wie der VAS und Lysholm-Score für AMIC sowie der Tegner Activity Score (TAS) und der subjektive und objektive IKDC für MACI und MFx. Zusätzlich wurden Röntgenbilder, MRT-Ergebnisse und der VAS für die MACI sowie der Lysholm-Score für die MFx als primäre Endpunkte herangezogen.

Klinische Wirksamkeit

keine stat. signifikanten Unterschiede zwischen AMIC+ und AMIC

Hinsichtlich der vergleichenden Wirksamkeit von AMIC+ gegenüber AMIC ergab das RCT zu keinem Zeitpunkt einen statistisch signifikanten Unterschied zwischen der Interventions- und der Kontrollgruppe in Bezug auf einen der Endpunkte. Dazu gehören die von den patient:innen-berichteten Ergebnisse zur Morbidität (KOOS-Schmerz und VAS), Funktion (KOOS-Symptome, ADLs und Sport und Freizeit; TAS und Lysholm) und der gesundheitsbezogenen Lebensqualität (KOOS QoL) sowie die von Kliniker:innen berichteten Ergebnisse zur Funktion (IKDC objective) und strukturellen Wiederherstellung (MRT, Defektgröße und -füllung).

keine stat. signifikanten Unterschiede zwischen AMIC+ und MACI, außer bei IKDC subjektive

Der Vergleich zwischen AMIC+ und MACI zeigte für die meisten Scores keine statistisch signifikanten Unterschiede zwischen den Gruppen, mit Ausnahme des subjektiven IKDC (Funktion) bei der letzten Nachuntersuchung (~60 Monate), der auf eine bessere Kniefunktion in der AMIC+ Gruppe im Vergleich zur MACI-Gruppe hinweist (Mittelwert ± SD: 82,52 ± 10,72 vs. 75,70 ± 9,85, p=0,015). Es gab keine signifikanten Ergebnisse für Morbidität (KOOS-Schmerz; VAS), einige funktionelle Maße (KOOS-Symptome, ADLs, Sport und Freizeit; TAS; Lysholm; IKDC objektiv) und die Lebensqualität

als PROM sowie die strukturelle Heilung (Defektfüllung, vollständige Integration) und Funktion (IKDC objektiv) beim letzten Follow-up. Unterschiede zwischen den Gruppen wurden bei der 24-monatigen Nachuntersuchung nicht analysiert.

stat. signifikanten Unterschiede zwischen AMIC+ und MFx hinsichtlich Morbidität und Funktion

Beim Vergleich von AMIC+ und MFx zeigten sich statistisch signifikante Gruppenunterschiede für KOOS-Schmerz und KOOS-Sport/Erholung beim 60-Monats Follow-up mit einem geringeren Schmerzniveau in der AMIC+-Gruppe (Median [IQR]: 95 [10] vs. 87 [31], $p=0{,}023$) und einer verbesserten Aktivität im täglichen Leben (Median [IQR]: 6 [1,5] vs. 4 [2], $p<0{,}001$). Darüber hinaus zeigte der IKDC objective statistisch signifikante Unterschiede zwischen den Gruppen zugunsten von AMIC+ ($p<0{,}001$).

Sicherheit

keine stat. signifikanten Unterschiede zwischen AMIC+ und Standardtherapien hinsichtlich der Sicherheit

In Bezug auf die Patient:innensicherheit wurde ein unerwünschtes Ereignis in der Interventionsgruppe AMIC+ versus AMIC beobachtet.

In der Studie AMIC+ versus MACI traten keine unerwünschten Reaktionen oder Infektionen auf, während in beiden Gruppen ein Fall von Debridement und Mobilisierung auftrat.

Beim Vergleich von AMIC+ mit MFx trat ein unerwünschtes Ereignis in der Interventionsgruppe auf.

Laufende Studien

5 laufende RCTs (4 AMIC; 1 AMIC+)

Derzeit laufen fünf RCTs zur Evaluierung von einzeitigen Verfahren zum Matrix-assistierten Knorpelersatz für Defekte im Knie. Vier RCTs zur Untersuchung von AMIC im Vergleich zur matrix-assistierten autologen Chondrozytentransplantation (n=80), MFx (n=185), technischem Knorpeltransplantat (n=150) beziehungsweise der modifizierten Mikrofrakturierung (n=100). Die Studien werden zwischen 2025 und 2032 abgeschlossen. Eine weitere RCT, die AMIC mit Knochenmarkaspiratkonzentrat (AMIC+) im Vergleich zur Mikrofrakturierung (n=200) untersucht, wird 2026 abgeschlossen. Die meisten Studien verwenden als primären Endpunkt die patient:innen-berichtete Endpunkte in Bezug auf Funktion oder Schmerz.

Diskussion

moderate bis sehr niedrige Vertrauenswürdigkeit der Evidenz

Insgesamt ist die Vertrauenswürdigkeit der Evidenz für die Wirksamkeit und Sicherheit von AMIC im Kniegelenk im Vergleich zu MFx als moderat bis niedrig und im Vergleich zu ACI als sehr niedrig einzustufen. Die Vertrauenswürdigkeit der Evidenz für die Wirksamkeit und Sicherheit von AMIC mit Knochenmarkaspiratkonzentrat (AMIC+) im Vergleich zu AMIC, MACI oder MFx ist als sehr niedrig zu bewerten.

Limitationen der Evidenz (AMIC):

hohes Verzerrungsrisiko aufgrund fehlender Verblindung

Unsicherheit über Langzeitfolgen

Die wesentlichen Limitationen der Evidenz bezüglich AMIC versus MFx umfassen hohe Verzerrungsrisiken in den meisten Studien. In diesem Zusammenhang sind fehlende Verblindung und hohe Drop-out-Raten sowie kurze primäre Nachbeobachtungszeiträume (meist bis zu 24 Monaten) in der Mehrzahl der Studien zu nennen. Es besteht außerdem Unsicherheit über die langfristige Wirksamkeit trotz einiger Langzeitdaten (bis zu 120 Monate), die aufgrund methodischer Schwächen anfällig für Verzerrungen sind. Zudem zeigt sich eine Heterogenität bezüglich Größe und Lokalisation der Knorpeldefekte, wodurch keine klaren Aussagen zur optimalen Auswahl von Patient:innen möglich sind. Die Variation in den verwendeten Matrix-Materialien verhindert Schlussfolgerungen zu optimalen Materialeigenschaften.

Limitationen der Evidenz (AMIC+): sehr niedrige Evidenzbasis

Die wesentlichen Limitationen der Evidenz bezüglich AMIC+ sind die sehr niedrige Evidenzbasis mit nur einer randomisierten und zwei nicht-randomisierten kontrollierten Studien sowie geringe Patient:innenzahlen in allen drei Studien. Für jeden Vergleich (AMIC, MACI, MFx) liegt jeweils nur eine Studie vor, mit sehr geringer Evidenzsicherheit über alle Endpunkte hinweg.

mögliche Verzerrung der Ergebnisse aufgrund von patient:innenberichteten Endpunkten

Die Mehrzahl der Endpunkte zur Wirksamkeit (Funktion, Lebensqualität, Schmerzen) wurde von den Patient:innen selbst berichtet, sodass Ergebnisse verzerrt sein könnten. Die Verwendung multipler validierter Outcome-Messungen für ein Ergebnis in Primärstudien erhöht zudem das Risiko der Multiplizität. Ebenso stellt der Endpunkt zur strukturellen Reparatur einen Surrogatendpunkt dar. Dennoch zeigten sich zwischen den Gruppen deutlich bessere Ergebnisse bei den AMIC-Patient:innen.

unzureichende Daten zur Langzeitwirkung

Im Vergleich zum LBI-HTA Bericht von 2019 konnten durch zusätzliche Evidenz Vorteile von AMIC gegenüber MFx festgestellt werden. Insgesamt fehlen dennoch zuverlässige Daten zur langfristigen Wirksamkeit und Sicherheit beider Verfahren (AMIC und AMIC+).

Schlussfolgerung

niedrige bis moderate Vertrauenswürdigkeit der Evidenz für AMIC verglichen mit MFx

Evidenz von niedriger bis moderater Vertrauenswürdigkeit deutet darauf hin, dass der einzeitige Matrix-assistierte Knorpelersatz (AMIC) bei der strukturellen Reparatur wirksamer ist als die Mikrofrakturierung, mit vergleichbaren oder besseren Ergebnissen für andere Endpunkte wie Funktion und Schmerz. Die Evidenz ist jedoch unzureichend, um verlässliche Aussagen über Langzeiteffekte über 24 Monate hinaus treffen zu können.

unzureichende Evidenz für AMIC vs. ACI und AMIC+ vs. Standardtherapie

Für Vergleiche mit anderen Verfahren ist die Evidenz derzeit unzureichend: für den Vergleich von AMIC mit autologer Chondrocytenimplantation liegt nur eine Studie mit geringer Stichprobengröße vor, während die Evidenz für AMIC mit Knochenmarkaspiratkonzentrat (AMIC+) auf drei Studien mit gemischten Ergebnissen beschränkt ist.

Neubewertung: 2033 (AMIC), 2028 (AMIC+)

Eine Neubewertung für AMIC wird für 2033 empfohlen. Für AMIC+ wird eine Überprüfung für 2028 nach Veröffentlichung der Ergebnisse der laufenden Studie empfohlen, ansonsten ebenfalls für 2033.

1 Background

Knorpel: spezialisiertes Bindegewebe in 3 Formen

Cartilage is a specialised connective tissue that exists in three main forms: hyaline cartilage, elastic cartilage, and fibrocartilage [1, 2]. Hyaline cartilage, also called articular cartilage, covers the articulating surfaces of bones within synovial joints and plays a crucial role in joint function and mobility [1, 2].

Hauptbestandteile sind extrazellulare Matrix + Chondrozyten

Articular cartilage consists of two main components: the extracellular matrix (ECM) and chondrocytes [2, 3]. The ECM is composed of water and collagen. Chondrocytes are the specialised cells of cartilage and operate in a low-oxygen environment.

Funktion ist reibungslose Gelenkbewegung

mechanische Kräfte können gesundheitsfördernd oder -schädigend sein

Cartilage serves several essential functions in joint health and mobility. It enables smooth articulation by preventing direct bone-to-bone contact, enabling fluid joint movement, and reducing impact [4]. The tissue excels at load distribution, acting as a weight-bearing surface that distributes mechanical forces evenly and prevents concentrated pressure points [5]. Mechanical stimulation has a dual effect on cartilage health: moderate loading proves beneficial, while excessive loading can be harmful [6].

begrenzte Regenerationsfähigkeit

Cartilage has limited regenerative capacity due to its avascular nature [2, 3, 7], but several factors influence its repair capabilities: Age plays a significant role, with younger individuals showing better healing capacity than older ones [8]. The severity of injury also impacts recovery, as smaller defects tend to heal better than larger ones [7]. The tissue's limited blood supply affects its ability to health and regenerate [2, 3, 7]. Additionally, inflammation has varying impacts, with acute inflammation supporting repair processes (as there is an increase in blood flow), while chronic inflammation leads to tissue destruction [5].

Notwendigkeit (nicht-)med. Unterstützung zur Knorpelregeneration

OP bei unwirksamer konservativer Behandlung

The incapacity of cartilage to regenerate necessitates the provision of support for cartilage regeneration subsequent to an injury or in the event of wear and tear. This support may be provided through medical interventions (i.e. drug treatment) or non-medical interventions (i.e. physiotherapy) to prevent symptoms and deterioration [9]. In instances where conservative treatment proves ineffective, surgical intervention for cartilage repair is generally undertaken [10].

1.1 Overview of the disease, health condition and target population[1]

Knorpelschaden oder osteochondraler Defekt

Surgical cartilage repair and regeneration treatments are based on either a cartilage/chondral defect (more broadly termed a chondral lesion) or an osteochondral defect (more broadly termed an osteochondral lesion). Osteochondral defects affect not only the cartilage but also the underlying bone [11]. The International Cartilage Regeneration & Joint Preservation Society (ICRS) categorised cartilage into five grades [12]:

ICRS Grading

- Grade 0 – Normal
- Grade 1 – Nearly Normal
  - Superficial lesions. Soft indentation and/or superficial fissures and cracks
- Grade 2 – Abnormal
  - Lesions extending down to <50% of cartilage depth
- Grade 3 – Severely Abnormal
  - Cartilage defects extending down to >50% of cartilage depth as well as down to calcified layer but not through the subchondral bone. Blisters are included in this grade.
- Grade 4 – Severely Abnormal

These pathological changes can develop in multiple synovial joints, such as the knee, hip or ankle joint [13-15]. Considering the particular interest of Austrian hospitals, the present assessment is focused on cartilage repair in the knee joint location, with the target group comprising adults.

74.815 Kniegelenk-OPs, fehlende Zahlen zum Knorpelersatz

In 2023, 74,815 knee joint operations were performed in Austria [16]. Operations on lower extremity tendons, bones and soft tissues were documented in 29,555 cases [16]. Specific data on cartilage repair in Austria have not been published, and the exact incidence of (osteo)chondral defects in general remains uncertain, especially in the absence of recent data.

61-63 % Defekt bei Knie-Arthroskopien ermittelt

Different reviews that examined knee arthroscopies between 1991 and 1999 found cartilage or (osteo)chondral lesions in 61 to 63% of cases [17, 18]. A study revealed that 193 out of 1,000 arthroscopies (19%) exhibited focal lesions [18]. Another literature review [19] of focal full-thickness cartilage defects in athletes' knees was conducted in 2009 and found an overall prevalence of 36% (range of studies from 2.4% to 75%), suggesting that approximately one-third of athletes are affected.

Ursachen: Traumata + Erkrankungen v. a. jüngere Erwachsene betroffen

Cartilage defects are primarily the result of traumatic events or diseases such as osteochondritis dissecans (OCD) and are more prevalent among younger demographics [20]. The mean age of arthroscopy studies exhibited a range from 43 years (range: 1-92 years) [17] to 39 years (SD, 14; range, 13-96) [18], while the mean age of athletics has been 33 years (range: 26-47 years) [19]. Most lesions in younger populations (43%-58%) occur in the weight-bearing femoral condyle, while patellar lesions occur in 11%-36% of cases and trochlear lesions in 6%-16% of cases [20].

[1] This section addresses the following assessment elements:
A0002 – What is the disease or health condition in the scope of this assessment?
A0023 – How many people belong to the target population?

One review indicates a mean (osteo)chondral lesion size of 2.1 cm^2 [18], while another shows high numbers of ICRS grades II (28.1%) and III (41.0%), whereas grade IV was detected in only 19.2% of 31,516 knee arthroscopies [17].

Full-thickness cartilage defects that fulfil the criteria for cartilage repair were detected in 11% of nearly 1,000 knees that underwent arthroscopy, with 55% larger than $2cm^2$ [21]. Notably, only a small proportion of identified defects require cartilage repair [20].

11 % erfüllen Kriterien zur Knorpelreparatur

Natural course[2]

Healthy articular cartilage comprises 95% ECM and 5% chondrocytes [22], with the cartilage undergoing constant internal remodelling during the course of life [15]. Chondrocytes (cartilage cells) react to changes in the ECM, triggered by degradation or mechanical demands, and contribute to maintaining cartilage composition and joint homeostasis through anabolic and catabolic metabolic processes [15, 22, 23]. It is evident that in addition to senescence (age-related cellular changes), abnormal forces, local diseases or systemic risk factors can prevent joint homeostasis and, therefore, the maintenance and restoration of matrix molecules, which in turn stimulates a vicious cycle of matrix degradation and inflammation of the synovium, resulting in continuous degeneration [15, 22, 23] and, frequently, to the development of osteoarthritis [24, 25].

gesunder Knorpel besteht aus extrazellulärer Matrix + Chondrozyten

Risikofaktoren verändern Gelenkhomöostase

kontinuierlicher Knorpelabbau; häufig Arthrose als Folge

Risk factors[3]

Chondral and osteochondral defects occur in all three compartments of the knee [20] and are often caused by **abnormal stress**, particularly traumatic knee injuries, chronic repetitive microtrauma or (over)loading, which occur with insidious symptoms [15, 20, 23]. These damages are particularly sports-related but can also arise from everyday activities [9]. In the case of acute trauma, the injury's intensity, duration and speed determine the cartilage tissue's reaction and, accordingly, whether a catabolic stress reaction and corresponding cartilage damage occur [15]. One example is injuries to the anterior cruciate ligament, which lead to damage to the medial meniscus and cartilage [22] and occur frequently in the general population with an incidence of 68.6 per 100,000 person-years [26]. Abnormal stress on the articular surface may also be caused by leg axis malalignment, and over time, this increases the risk of patellar dislocation associated with traumatic cartilage damage [15, 20].

Fehlbelastung: traumatische/multiple mikrotraumatische Verletzungen, Überbelastung

In addition to abnormal stress, there are several **systemic risk factors**. These include age, genetic abnormalities and predisposition to early deterioration, body mass index (BMI) and acquired metabolic factors such as avascular necrosis [20, 23]. Age plays a critical role in the development of (osteo)chondral defects and the indication for cartilage repair [27], e.g. a significant association exists between age and loss of tibial cartilage volume [28].

systemische Risikofaktoren: Alter, genetische Anomalien + Prädisposition, BMI, metabolische Faktoren

[2] This section addresses the following assessment element:
A0004 – What is the natural course of cartilage defects?

[3] This section addresses the following assessment element:
A0003 – What are the known risk factors for cartilage defects?

Finally, **localised diseases**, notably OCD or degenerative diseases, as well as muscle weakness and joint hyperlaxity, can also cause cartilage destruction [20, 22, 23]. Degenerative diseases are characterised by progressive destruction of the structure of the affected tissue and may affect other joint structures, as is the case for gonarthrosis [22, 29].

lokale Erkrankungen: v. a. Osteochondritis dissecans (OCD) + degenerative Erkrankungen

OCD is a "focal, idiopathic alteration of subchondral bone with risk for instability and disruption of adjacent articular cartilage that may result in premature osteoarthritis" [30]. The prevailing hypothesis is that OCD triggers the development of loose bodies within the joint matrix in the absence of overt trauma [31]. In contrast to cartilage degradation due to external trauma, the process of the disease begins deep beneath the joint surface [11]. The exact aetiology of this condition remains unclear. Local ischaemia, obesity, detachment of accessory epiphyseal ossification centres, repeated microtrauma, endocrine fractures, and familial and genetic predisposition are discussed as possible risk factors [32, 33]. The condition's incidence ranges from 2.3 to 31.6 cases per 100,000 people, primarily affecting the knee and being most prevalent among adolescents aged 13-17 [32].

Krankheitsbeginn tief unter Gelenkoberfläche; Ätiologie unklar

OCD: Entwicklung loser Körper im Gelenk ohne externes Trauma

Consequences[4]

Irrespective of the aetiology of cartilage defect, whether it be acute trauma, OCD or other factors, the majority of patients experience swelling, pain, dysfunction, and a consequent decrease in quality of life (QoL) [32, 34, 35]. Preoperatively, patients with focal cartilage defects demonstrate significantly worse performance on the subscale for QoL of the Knee Injury Osteoarthritis Outcome Score (KOOS) than patients with a history of cruciate ligament defect [35]. Untreated cartilage defects can lead to early-onset osteoarthritis, characterised by progressive pain and functional impairment [24, 36]. Furthermore, a vast majority of the patients suffering from defect cartilage of the knee are in their productive age. As a result, some of the patients are incapacitated to work, which can be assumed to result in additional societal costs [37].

Schwellungen, Schmerzen, Einschränkung der Lebensqualität

unbehandelt: Arthrose + Funktionseinschränkung

[4] This section addresses the following assessment elements:
A0005 – What is the burden of disease for the patients with cartilage defects?
A0006 – What are the consequences of cartilage defects for the society?

1.2 Current clinical practice[5]

Diagnosis of cartilage defects

4 Leitlinien zu Knorpeldefekten identifiziert

One international guideline for the diagnosis and treatment of OCD [38], one for meniscal and articular cartilage lesions [39], one Swiss guideline for cartilage defects [15] and one German guideline for the treatment of focal cartilage defects of the knee joint [40] were identified. According to the guidelines, the diagnostic process begins with obtaining detailed medical history, including comprehensive information about accident history and family medical background. This is followed by a physical examination, including inspection (swelling of the joint, gait, etc.) and palpation (pressure pain, extrusion in the joint, etc.). The next step involves diagnostic imaging, including X-rays and/or magnetic resonance imaging (MRI). Alternative imaging techniques may also be employed, including ultrasound, computed tomography or arthroscopy [15, 38, 39].

Management of cartilage defects

Behandlungsziele sind Schmerzreduktion, Wiederherstellung der Beweglichkeit und die Vermeidung einer Arthrose

The treatment of cartilage defects aims to achieve several key objectives: reducing pain, restoring joint mobility, rehabilitating the affected area, preventing or slowing osteoarthritis progression, and avoiding complete joint replacement [15, 37-39]. Treatment typically begins with conservative management, which encompasses physical therapy, controlled weight-bearing exercises, nutritional supplementation, and pain management through medications such as nonsteroidal anti-inflammatory drugs (NSAIDs). Injectable treatments, including hyaluronic acid and platelet-rich plasma, may also be administered.

Unterscheidung der Ziele: alleinige Symptomreduktion oder zusätzliche Knorpelwiederherstellung

According to the National Institute for Health and Care Excellence (NICE), surgical procedures can be categorised into two main groups [41]. The first group focuses on symptom relief and includes debridement, osteotomy, and knee replacement. The second group aims for symptom relief and cartilage restoration, comprising marrow stimulation techniques, mosaicplasty, focal articular resurfacing implants and (matrix-induced) autologous chondrocyte implantation.

keine universelle Behandlungsmethode empfohlen

The selection of appropriate treatment is highly individualised, as no single surgical approach is universally recommended in international medical guidelines [15, 37-39]. The choice depends on various factors, including the size and location of the defect, the patient's age, and the severity of symptoms. Some recommendations include surgery in general for both skeletally mature and immature patients with unstable OCD (low level of evidence) provided by the American Academy of Orthopaedic Surgeons (AAOS) [38]. The Swiss Society for Arthroscopy and Joint-Surgery [15] as well as the German Orthopaedic and Trauma Society provide [40] size-based recommendations, sug-

[5] This section addresses the following assessment elements:
A0024 – How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025 – How are chondral defects currently managed according to published guidelines and in practice?
A0011 – How much is AMIC utilised?
A0006 – What are the consequences of cartilage defects for the society?

gesting bone marrow stimulation for defects up to 2 cm^2, bone marrow stimulation with cell-free scaffolds for defects between 1 and 4.5 cm^2, and autologous chondrocyte transplantation for lesions larger than 2 cm^2.

Utilisation of one-stage matrix-assisted cartilage repair

10 einzeitige Matrix-assistierte Knorpelersatz-Operationen im vergangenen Jahr

In the past year, submitting hospitals reported performing ten one-stage matrix-assisted cartilage repair procedures and estimate an increase to approximately 30 procedures in the coming year, though actual numbers across Austria may vary. Specifically, for one-stage cartilage repair procedures with bone marrow aspirate concentrate (BMAC), between two and five procedures were performed currently and are expected to stay at five procedures annually.

1.3 Features of the intervention[6]

Features of the assessed intervention

One-stage matrix-assisted cartilage repair (AMIC- Autologous matrix-induced chondrogenesis)

einzeitiger Matrix-assistierter Knorpelersatz=Autologe Matrixinduzierte Chondrogenese (AMIC)

The one-stage matrix-assisted cartilage repair[7], marketed as "autologous matrix-induced chondrogenesis" (AMIC®, Ed. Geistlich Söhne AG, Switzerland), combines microfracture with matrix or scaffold placement to cover the cartilage defect. The scaffold, constructed from biomaterials such as collagen or hyaluronan, is designed to capture cells migrating from the subchondral layer. This matrix serves two key functions: it provides mechanical stability and may promote chondrogenic differentiation and cartilage regeneration[27]. It was introduced in 2011 and is not a newly discovered technique [42].

Matrix als temporäre Platzhalter in fester Form oder als Gel

Used matrices are cell-free scaffolds, such as porcine collagen matrix [37]. However, scaffolds come in various forms, from solid materials to injectable gels, depending on the product. They can be custom-sized by cutting or are available in standard dimensions [41]. The attachment method varies by scaffold consistency: press-fit [43], suturing or glueing (e.g. with fibrin glue) [44], or injection [45]. In this review, studies using either solid or injectable scaf-

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[6] **B0001** – What is AMIC, (M)ACI and MFx?
A0020 – For which indications has AMIC received marketing authorisation or CE marking?
B0002 – What is the claimed benefit of AMIC in relation to (M)ACI and MFx?
B0003 – What is the phase of development and implementation of AMIC, (M)ACI and MFx?
B0004 – Who administers AMIC, (M)ACI, and MFx and in what context and level of care are they provided?
B0008 – What kind of special premises are needed to use AMIC, (M)ACI, and MFx?
B0009 – What supplies are needed to use AMIC, (M)ACI, and MFx?
A0021 – What is the reimbursement status of AMIC?

[7] There are several terms used for this procedure, including matrix-augmented bone marrow stimulation and collagen-augmented chondrogenesis. As AMIC (Autologous Matrix-Induced Chondrogenesis) is the most commonly used term in the literature, we will use this term throughout the review.

folds will be considered in order to provide a comprehensive assessment of both available techniques. Table 1-1 provides an overview of products and CE-markings.

Anreicherung der Matrix mit Zellsuspensionen möglich

The scaffold can be enhanced with additional cell suspensions such as platelet-rich plasma, umbilical blood-derived blood, mesenchymal fat stem cells, and BMAC. In this review, we exclusively focus on scaffolds without any additional material and the addition of BMAC.

Eingriff mit anderen Operationen kombinierbar

AMIC can be performed alongside other surgical procedures, including high tibial osteotomy, meniscal treatments, or anterior cruciate ligament surgery [41].

möglicher Vorteil in der Knorpelreparatur

Proponents of AMIC claim two main benefits: improved cartilage repair (particularly visible in MRI findings) and the advantage of requiring only one surgical procedure, potentially leading to faster recovery [41].

mögliche Komplikationen u. a. Infektionen, septische Arthritis, Thrombosen

Potential complications include surgical failure requiring revision surgery, muscle atrophy, infection, septic arthritis, arthrosynovitis, deep vein thrombosis, hematoma, swelling, and effusion. Patients may also experience stiffness, reduced range of motion, joint adhesion, and knee pain [41].

Bone marrow aspirate concentrate (BMAC)

Knochenmarkaspiratkonzentrat (BMAC – bone marrow aspirate concentrate)

BMAC is a cellular treatment product that promises to offer the advantage of immediate, one-stage use without requiring cell cultivation. It is typically harvested from the iliac crest due to its higher concentration of progenitor cells, with quality enhanced through multiple-site aspiration and specific collection techniques [46].

enthält Stammzellen und Wachstumsfaktoren

Through density gradient centrifugation, BMAC concentrates several key cellular components, including white blood cells, platelets, mesenchymal stem cells (MSCs), and hematopoietic stromal cells. While MSC concentration remains low (0.001%-0.01%), BMAC's therapeutic benefits are believed to come from its rich growth factor content. Once harvested, the BMAC can be injected into the damaged area or combined with a matrix-based scaffold [47].

wird auf Matrix aufgetragen

möglicher Nutzen durch antientzündliche Eigenschaften

The treatment's effectiveness may be further enhanced by its anti-inflammatory properties, which help regulate cellular processes, support tissue regeneration, and reduce inflammation, anticipating BMAC to be particularly beneficial for treating cartilage defects. Clinical applications include use with scaffolds, clot transformation, mini arthrotomy implantation, and as an adjunct to other procedures like microfracture or bone grafting [46].

Table 1-1: Manufacturers and products of intervention and comparator

	Manufacturer	Product	Characteristics	Class/GMDN Code	CE marking	Reference
Intervention (AMIC, AMIC+)	Smith & Nephew GmbH, USA[8]	BST-CarGel®	Gel consists of a chitosan solution (a natural polymer) and a buffer.	NR	Yes (2014)	[48]
	Arthro Kinetics AG, Austria	CaReS®-1S	A collagen type I matrix for the treatment of chondral lesions.	Class III/EN ISO 13485	Yes (2024)	Information provided by manufacturer
	Geistlich Pharma, Switzerland	Chondro-Gide®[9]	A bilayer matrix made from collagen type I/III for the treatment of traumatic chondral and osteochondral lesions.	Class III	Yes (2010)	[50]
	BioTissue Technologies GmbH, Switzlerand	Chondro-tissue®	The matrix is made from polyglycolic acid fleece and freeze-dried sodium hyaluronate for the treatment of chondral lesions.	NR	Yes (2007)	[51]
	Regentis Biomaterials Ltd., Israel	GelrinC®	A hydrogel of polyethylene glycol di-acrylate (PEG-DA) and denatured fibrinogen, crosslinked with UVA light in-situ, for the treatment of chondral defects.	ISO 13485	Yes (2013)	[52]
	Anika Therapeutics, Inc., USA	Hyalofast®	A biodegradable, hyaluronan-based (HYAFF) scaffold is intended to repair chondral or osteochondral lesions.	Class III	Yes (2013)	[53]
	Fin-Ceramica Faenza S.p.A., Italy	MaioRegen™	A multi-layer scaffold: the superficial layer consists of deantigenated type I equine collagen and resembles the cartilaginous tissue, while the lower layer consists mostly of magnesium-enriched hydroxyapatite (Mg-HA) and stimulates the subchondral bone structure	Class III	Yes (2023)	Information provided by manufacturer [54]
	Bioteck S.p.A., Italy	MeRG®	A microfibrilla collagen membrane that is inserted in the chondral lesion after microfracture	NR	Yes (2012)	[55]
	Meidrix GmbH, Germany	Chondro-filler®	Biological cartilage implant made of high-purity, native collagen, available as a cell-free matrix in the form of a gel or a liquid.	Class III	Gel: Yes (2012) Liquid: Yes (2013)	Information provided by manufacturer
	Oligo Medic, Canada	JointRep™	Injectable hydrogel from chitosan/glucosamine to fill in cartilage defects	NR	Yes (2013)	[56]
Comparator (MACI)	BiotTissue Technology GmbH, Switzerland	BioSeed®-C	Autologous three-dimensional chondrocyte transplantation.	NR	Yes (year unknown)	[51]
	CO.DON AG	Spherox®	Matrix-associated endogenous three-dimensional cartilage cell transplantation	NR	Authorised as ATMP (07/2017)	[57, 58]
	Histogenics®	NeoCart®	Cells seeded on a unique three-dimensional collagen scaffold and cultured under exacting conditions of high pressure, oxygen concentration and perfusion in their proprietary Tissue Engineering Processor (TEP).	NR	NR	[59]
	Anika Therapeutics, Inc., USA	Hyulograft C autograft	Composed of cultured autologous chondrocytes seeded on a hyaluronan-based scaffold	NR	No (off the European market since 2013)	[60]
	Octane Biotherapeutics (BioTx) Inc., USA[10]	Novocart® 3D	Biphasic, three-dimensional collagen-based matrix inserted after microfracture technique.	NR	Yes (year unknown)	[61]
		NovocartTM Inject	Two-component injection system. The first component comprises the in vitro culture-expanded chondrocytes, and the second component a bis-thio-polyethylene-glycol crosslinker.	NR	NR	[58, 61]

Abbreviations: AMIC … autologous matrix-induced chondrogenesis; AMIC+ … autologous matrix-induced chondrogenesis with BMAC; ATMP-; Advanced Therapy Medicinal Products; GMDN … Global Medical Device Nomenclature; MACI … matrix-induced autologous chondrocyte implantation; NR … not reported; USA … United States of America.

[8] Former manufacturer was Piramal Enterprises Ltd, Canada.

[9] Also used for the autologous chondrocyte implantation in Fossum [49].

[10] Former B.Braun, venture OCTANE, partner: TETEC AG, Germany.

Features of the comparators

einzeitige und zweizeitige Verfahren als Standardtherapie

Standard of care consisting of one-stage procedures, such as microfracture and osteochondral autologous transplantation (OAT) and two-stage procedures, comprising (matrix-induced) autologous chondrocyte implantation (MACI and ACI), are considered comparators in this assessment.

Mikrofrakturierung (MFx, einzeitiges Verfahren)

Microfracture (MFx) is a standard one-stage cartilage repair technique developed by Steadman in the late 1980s to early 90s [62]. During this procedure, small holes are made through the bone (perforation), usually with an awl, whereby stromal cells are animated to proceed to the damaged area. For this surgery, no matrix or scaffold is used [10, 63]. This procedure is claimed to be more effective in smaller lesions (≤2cm^2, [10, 37].

osteochondrale autologe Transplantation (OAT, einzeitiges Verfahren)

Osteochondral autologous transplantation (OAT) is also known as mosaicplasty. During this procedure, cylindrical osteochondral grafts are harvested from low-weight-bearing areas of the femoral condyle and implanted into the cartilage defect. It is also performed in a single operation, typically as part of an arthroscopy. Alternatively, osteochondral allograft transplantation exists, where a donor can provide larger amounts of cartilage and parts of the bone. This procedure is more commonly used in adolescents [10].

(matrixinduzierte) autologe Chondrozytenimplantation (MACI/ACI, zweizeitge Verfahren)

Autologous chondrocyte implantation (ACI) is a two-step cartilage repair procedure introduced in the 1990s [64]. In the first step, intact cartilage is harvested arthroscopically and cultured for some weeks. If there are enough cells to re-implant, the cultured cells are implanted in a second surgery [10, 37, 46]. This procedure has been modified over the past few years and can also be combined with a matrix or scaffold, called matrix-induced autologous chondrocyte implantation (MACI) [27]. Some scaffolds used for AMIC can also be used for the MACI procedure (depending on the manufacturer (see Table 1-1). Both ACI and MACI are indicated for larger defects (>2 cm^2) [10, 37, 46].

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

OP durch Orthopäden oder Unfallchirurgen

The intervention and control procedures are performed by orthopaedic or trauma surgeons assisted by qualified medical staff. The facility must have a fully equipped operating room, an arthroscopic tower, and the implantable matrix material. For the BMAC procedure, additional requirements include a specialised syringe for bone marrow harvesting and centrifugation equipment (information provided by the submitting hospitals).

Regulatory and reimbursement status

derzeit keine volle Rückerstattung nach AMIC oder AMIC mit BMAC (AMIC+)

There are established codes in the Austrian hospital benefit catalogue for mosaicplasty, a one-stage procedure, and implantation of cultivated autologous chondrocytes, a two-step procedure (open NF131, or arthroscopically NF132). No distinct code exists for AMIC or AMIC with BMAC augmentation (AMIC+). Hence, these procedures are currently not fully reimbursable services.

2 Objectives and Scope

Anpassung der Forschungsfragen (AMIC und AMIC+)

The AMIC procedure was already studied in a report by the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA) in 2019 [37]. This report builds on the search strategy of the previous report and additionally analysis AMIC+ procedures. However, we focused on AMIC and AMIC+ procedures only in the knee joint.

2.1 PICO question

PIKO-Frage

Is the one-stage matrix-assisted cartilage repair with and without bone marrow aspirate concentrate in the knee as safe as standard therapy and more effective in patients with indications for cartilage knee surgery concerning physical function, pain and other patient-centred outcomes (e.g. quality of life)?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Adult patients with indications for surgical cartilage repair in the knee ■ Grade III to IV (Outerbridge classification) localised cartilage damages/defects/disorders in the knee ■ Grade III to IV (ICRS classification) (osteo)chondral lesions ■ Defect size >1cm^2 Indications including but not limited to: **ICD11 Codes:** FA34.Y other joint derangements, FB82 Chondropathies; FB82.0 Chondromalacia; FB82.1 Osteochondrosis or osteochondritis dissecans; FB82.Y other specified chondropathies; FB82.Z chondropathies, unspecified; FB8Y other specified osteopathies or chondropathies; FB8Z Osteopathies or chondropathies, unspecified; NC93.4 Tear of articular cartilage of knee **Contraindications:** ■ Inflammatory diseases ■ Allergies of the used material(s) ■ Malposition of the knee ≥5 degrees (if no corrective osteotomy is performed) ■ Obesity ■ Meniscal absence ■ Generalised osteoarthritis **MeSH Terms:** cartilage A02.165, A10.165.382; cartilage articular A02.165.407.150, A02.835.583.192; cartilage diseases C05.182, C17.300.182; osteochondritis dissecans C05.116.791.668 **Rationale:** Informed by information provided by the submitting hospital and scoping of the literature. Note: the population may be grouped, e.g. according to defect size.

<table>
<tr><td>Intervention</td><td>One-stage matrix-assisted cartilage repair (without bone marrow aspirate concentrate (BMAC)) in the knee (further referred to as AMIC)
Alternative terms:
■ Autologous matrix-induced chondrogenesis (AMIC)
■ Cell-free matrix-induced chondrogenesis
■ Cell-free (collagen) matrices/matrix
Product names (including but not limited to):
■ Chondro-Gide® (Geistlich Pharma, Switzerland)
■ BST-CarGel® (Smith & Nephew GmbH)
■ CaReS®-1S (Arthro Kinetics AG, Germany)
■ Chondrotissue® (BioTissue Technologies GmbH, Switzerland)
■ GelrinC® (Regentis Biomaterials Ltd., Israel)
■ Hyalofast® (Anika Therapeutics, Inc., USA)
■ MaioRegen™ (Fin-Ceramica Faenza S.p.A., Italy)
■ MeRG® (Bioteck S.p.A., Italiy)
■ Chondrofiller® (Meidrix Biomedicals GmbH, Germany)
■ JointRep™ (Oligo Medic, Canada)</td><td>One-stage matrix-assisted cartilage repair with bone marrow aspirate concentrate (BMAC) in the knee (further referred to as AMIC+)
Alternative terms:
■ Autologous matrix-induced chondrogenesis (AMIC) + BMAC
Product names (including but not limited to):
■ Chondro-Gide® (Geistlich Pharma, Switzerland)
■ Hyalofast® (Anika Therapeutics, Inc., USA)
■ MeRG® (Bioteck S.p.A., Italy)</td></tr>
<tr><td></td><td colspan="2">MeSH Terms: chondrogenesis G07.345.500.325.377.625.180, G11.427.578.180; bone marrow A15.382.216, tissue scaffolds E07.206.627, E07.695.825
Rationale: Informed by information provided by the submitting hospital and a scoping search of the literature.</td></tr>
<tr><td>Control</td><td colspan="2">Surgical management: standard of care including but not limited to microfracture surgery/microfracture standard of care and autologous chondrocyte implantation/transplantation (open surgery, arthroscopy)
Excluded: Studies comparing the performance of different cell suspensions (e.g., BMAC vs. umbilical cord blood-derived mesenchymal stem cells)
Rationale: informed by information provided by the clinical expert and the scoping literature.</td></tr>
<tr><td>Outcomes</td><td colspan="2">Including trials should report at least one of the following outcomes for efficacy and one for safety.
The inclusion of additional outcome measures will not result in exclusion.</td></tr>
<tr><td>Efficacy</td><td colspan="2">■ Patient-reported outcome measures
■ Physical function, activity level and symptoms (e.g. International Knee Documentation Committee (IKDC), Tegner Activity Scale, Lysholm score, Knee injury and Osteoarthritis Outcome Score (KOOS)
■ Pain (e.g. Visual Analogue Scale (VAS))
■ Health-related quality of life (e.g. SF-36)
■ Necessity of total joint replacement
■ Surrogate outcome: structural repair
Rationale: Informed by a scoping of the literature and expert opinions.</td></tr>
<tr><td>Safety</td><td colspan="2">■ Any adverse events
■ Any serious adverse events</td></tr>
<tr><td>Study design</td><td colspan="2">One-stage matrix-assisted cartilage repair: Randomised controlled trials.
One-stage matrix-assisted cartilage repair + BMAC: In the absence of sufficient data from randomised controlled trials, prospective non-randomised controlled trials, including ≥20 patients, will be considered.
Excluded: Non-peer-reviewed studies, narrative reviews, letters to the editor and author responses, case reports, conference abstracts.</td></tr>
</table>

3 Methods

EUnetHTA Core Model® und methodische Leitlinie

The European Network for Health Technology Assessment (EUnetHTA) Core Model® [65] and methodological guidance documents developed by the Health Technology Assessment Regulation [66] methods subgroup were used as reporting standards.

OSF und AIHTA Protokoll

The systematic review was pre-registered on the Open Science Framework platform [67] and followed a generic AIHTA protocol [57]. There were only minor protocol deviations, including additional exclusion criteria for the comparator and a specification of the study design for PICO 2. More specifically, studies that compared different cell suspensions (e.g., BMAC vs. umbilical cord blood-derived mesenchymal stem cells) were also excluded and, in addition to randomised controlled trials (RCTs), only prospective controlled non-randomised controlled trials (NRCTs, including ≥20 patients) were considered for studies that investigated AMIC+.

3.1 Research questions

EUnetHTA Core Model®

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment. Please refer to Appendix (Table A-16 to Table A-19) for the detailed research questions.

3.2 Preliminary search

Suche nach systematischen Übersichtsarbeiten als Update-Grundlage

As a first step, a focused search for systematic review on the defined PICO was conducted to identify existing systematic reviews (SRs) that can eliminate the need for a separate comprehensive review. These reviews can, therefore, be used as the basis for an update, provided they address the PICO of this report and have a low risk of bias. If one or more such basic reviews were available, an additional search for RCTs for the period not covered by the basic reviews was conducted in a second step. Otherwise, the search for RCTs was conducted without time restriction.

Bewertung der Studienvertrauenswürdigkeit von 4 relevanten Reviews

The systematic search, conducted in Embase, yielded nine potentially relevant reviews, which were then screened by two independent reviewers. Four of these reviews were found to align with the specified PICO and were consequently assessed by two independent reviewers using the ROBIS (Risk Of Bias In Systematic Reviews) tool [68] (see Appendix Table A-1).

3.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

None of the reviews identified in the preliminary search were suitable as a comprehensive basis for an update (rationales listed in Table A-1). A systematic literature search was therefore conducted on the 18th and 19th December 2024 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International HTA Database (INAHTA)

systematische Suche: 828 Treffer (nach Deduplizierung)

The systematic search was limited to articles published in English or German. Furthermore, conference abstracts in Embase and study records from study registers in the Cochrane Library were excluded from the search. After deduplication, an overall of 828 citations were included. The specific search strategy employed can be found in the Appendix.

150 Hersteller-Einreichungen

Manufacturers from the most common products (n=10) submitted 150 publications, of which 64 new citations were identified.

Handsuche: 0 Treffer; Vorgängerbericht = 1 Treffer

Handsearching and reviewing the reference list resulted in eight records being found, with one relevant hit added from the previous report [37]. Overall, there were no additional hits after deduplication.

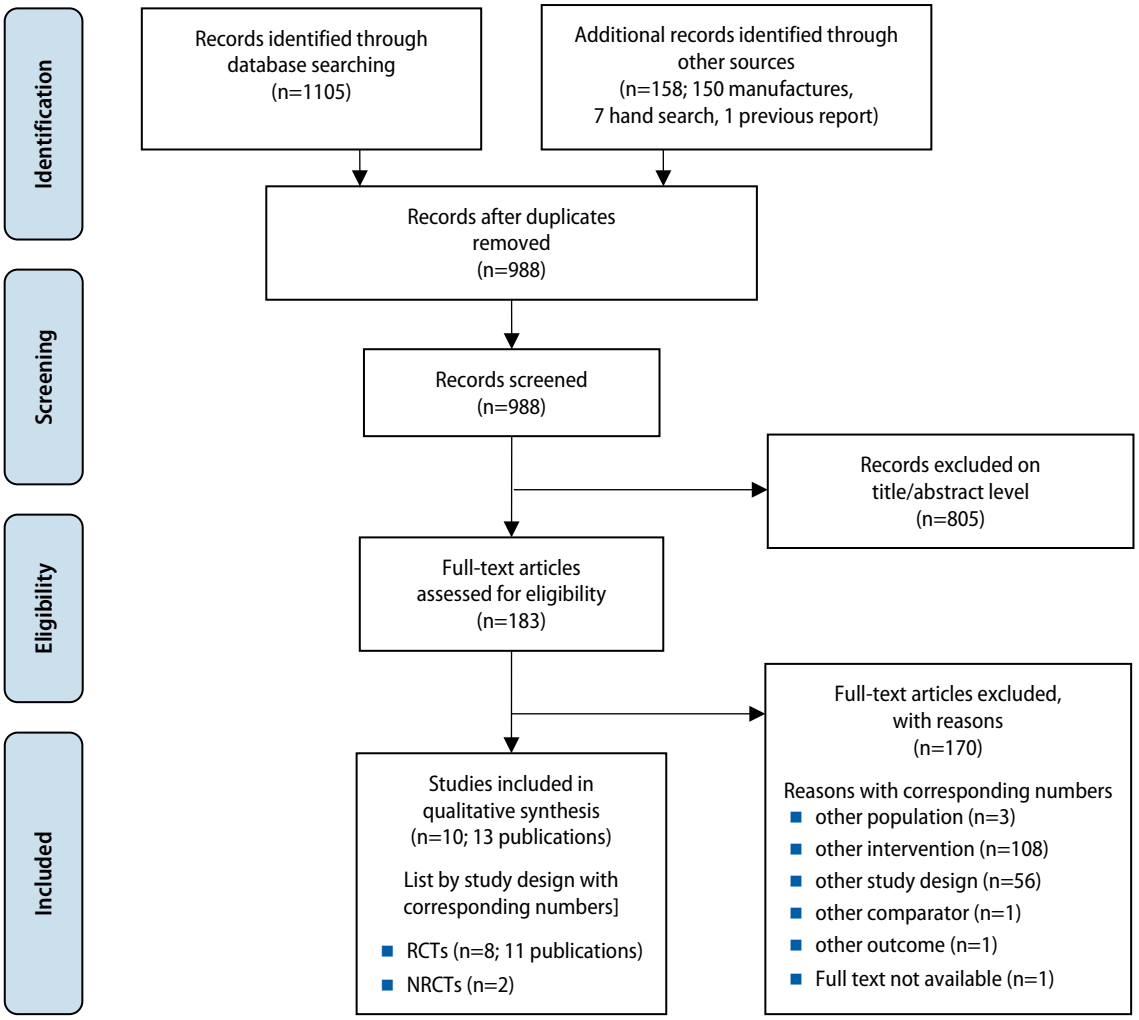
Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on 10.01.2025), resulting in 20 potentially relevant hits. The six relevant studies are summarised in the Appendix (Table A-14 and Table A-15).

3.3.1 Flow chart of study selection

Overall, 988 hits were identified. Two review authors independently screened titles and abstracts (JP, GG) and full-text articles (JP, MR) of potential studies according to the eligibility criteria (chapter 2.2). We resolved any disagreement through discussion or consultation of all involved authors. The selection process is displayed in Figure 3-1.

insgesamt 988 Publikationen identifiziert; Literaturauswahl: 10 Studien (13 Publikationen) eingeschlossen



Abbreviations: NRCT … non-randomised controlled trial; RCT … randomised controlled trial.

Note: Five of the 11 randomised control trial publications were already included in the last update report in 2019 [37].

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.3.2 Analysis

Datenextraktion: 2 unabhängige Wissenschafter:innen

Relevant data from included studies were extracted into piloted data extraction tables and cross-checked by a second author for accuracy. We used Web Plot Digitizer [66] for data available only in graphical format and rounded all extracted values to one decimal place. Where not directly reported, we calculated missing standard deviations, confidence intervals and mean differences using standard formulae, where sufficient data were available from the original studies to allow these estimates.

interne Validität: RoB v2 (RCTs) + ROBINS-I (NRCTs)

The internal validity of included studies was assessed using the Cochrane Risk of Bias (RoB) tool v.2 [69] for RCTs and the Risk Of Bias In Non-Randomised Studies Of Interventions (ROBINS-I) tool for NRCTs [70], see Appendix Tables Table A-6 and Table A-7. We evaluated RoB per endpoint but dichotomised the RoB assessment tables into patient-reported and clinical endpoints, as RoB assessments were not different within these endpoint-clusters.

Vertrauenswürdigkeit in die Evidenz mit GRADE erfasst

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) scheme to rate the certainty of evidence [71]. For each endpoint, the optimal information size (OIS) required to assess imprecision was calculated using Claude AI [72] and based on $\alpha=0.05$ (two-sided), $\beta=80\%$ and the minimal clinically important difference (MCID). Each working step was performed by one reviewer and validated by another (MR, JP, GG). Any disagreements were resolved by consensus.

3.3.3 Synthesis

narrative Synthese Fokus: 24 Monate und Langzeit-Follow-up

We addressed each research question in a narrative format, supported by GRADE evidence tables provided in Appendix Table A-8 to Table A-12. As long-term results are particularly important for the efficacy and safety of cartilage repair, we focused on 24-month and long-term follow-up. If a 24-month follow-up was unavailable, the longest follow-up <24 months was reported. The reporting is divided accordingly into ≤24 months and >24 months, i.e. the long-term results reported at each time point >24 months.

random-effect Metaanalyse mit Heterogenitätsbewertung

A random-effects meta-analysis was conducted using the 'meta' package in RStudio [73] to pool mean differences between treatment groups using the inverse variance method. Meta-analyses were performed when at least three studies reported results using the same outcome measure at comparable time points. Between-study heterogeneity was assessed using the I^2 statistic.

A comprehensive summary of the findings is presented in Table 5-1 to Table 5-5.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

entscheidende Endpunkte für Wirksamkeit

The following outcomes were defined as *critical* to deriving a recommendation:

- Physical function, activity level
- Health-related quality of life
- Pain
- Necessity of joint replacement
- Structural repair

körperliche Funktion und Aktivitätslevel

Physical function and activity level can be measured by different scores, including patient-reported outcome measurements (PROMs) and clinician-reported outcome measurements (CROMs):

Knee Injury and Osteoarthritis Outcome Score (KOOS) – höhere Punktzahl bedeutet bessere Funktion

Knee Injury and Osteoarthritis Outcome Score (KOOS) consists of 42 items in five separately scored domains (1) Pain (nine items); (2) Other symptoms (seven items); (3) Function in daily living (ADL) (17 items); (4) Function in sport and recreation (sport/rec) (five items); (5) Knee-related QoL (four items). A Likert scale is used, and all items have five possible answer options, scoring from 0 (no problems) to 4 (extreme problems). Each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0-100 scale, with 0 representing extreme problems and 100 representing no problems [74]. Minimal Clinical Important Difference (MCID) for total KOOS can be estimated as 12, the subscale pain 12 as well, and the subscale QoL 14 based on the results of a systematic review on MCIDs of PROMs [75].

International Knee Documentation Committee (IKDC) – höhere Punktzahl bedeutet bessere Funktion

International Knee Documentation Committee (IKDC) Subjective Knee Form, designed to assess patient's level of knee disorders. A patient-reported outcome measure, which contains sections on knee symptoms (seven items), function (two items), and sports activities (two items). Scores range from 0 points (lowest level of function or highest level of symptoms) to 100 points (highest level of function and lowest level of symptoms) [76]. MCID was estimated after articular cartilage repair surgery as 16.7 based on the analysis of ROC curves [76].

Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) – niedrigere Punktzahl bedeutet bessere Funktion

Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) is a self-administered questionnaire consisting of 24 items divided into three subscales: (1) Pain (five items); (2) Stiffness (two items); (3) Physical function (17 items). The WOMAC is available in two formats: the visual analogue scale (VAS) and five Likert boxes [77]. Concerning the VAS-like WOMAC, scores have a maximum value of 50 for pain, 20 for stiffness and 170 for function (items rated from 0 to 10). High scores indicate worse pain, stiffness and physical function. [77]. MCID for the WOMAC total is 10, subscale function 9, subscale pain 11, subscale stiffness 8 (anchor-based methodology) [78].

Modified Cincinnati Knee Rating System (mCKRS) – höhere Punktzahl bedeutet bessere Funktion

Modified Cincinnati Knee Rating System (mCKRS) evaluates knee function through 12 questions, with 8 of these included in the summary score. The assessment focuses on key aspects of knee health, including pain, swelling, function and activity levels. Scores range from 0 to 100, where 100 indicates the best knee function, while 0 represents the worst knee function [79].

The Lysholm scoring scale is a patient-reported outcome measure consisting of eight items measuring pain, instability, locking, swelling, limp, stair climbing, squatting, and need for support. Each question is scored on a scale from 0 to 10, with a total possible score of 100. Higher scores indicate better function [80]. The MCID is 25 for the Lysholm score[81].

Lysholm Scoring Scale – höhere Punktzahl bedeutet bessere Funktion

The Tegner Activity Scale (TAS) is a patient-reported outcome measure assessing (sporting) activity for people with knee injuries. Scores range from 0 (indicating disability caused by the injury) to 10 (representing the ability to play competitive sport) [41].

Tegner Activity Scale (TAS) – höhere Punktzahl bedeutet bessere Funktion

Short Form Health Survey (SF-36) is a patient-reported assessment tool that measures overall health status. It uses eight different scoring categories, each calculated by combining weighted responses to related questions: Vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The scores are converted to a standardised 0-100 scale, where 0 indicates maximum disability, and 100 represents optimal health with no disability[82]. Based on a systematic review of MCIDs of PROMs, the MCID for SF-36 total is 5, for the subscale physical functioning 7, and for the subscale mental health 4 [75].

Short-Form Health Survey (SF-36) – höhere Punktzahl bedeutet bessere Funktion

Health-related quality of life (HRQoL) can be measured by different scores (PROMs):

Knee Injury and Osteoarthritis Outcome Score (KOOS): One subscale of the KOOS concerns knee-related quality of life (QoL) (four items). A Likert scale with five possible answer options is used, scoring from 0 (no problems) to 4 (extreme problems)[74]. See information above.

Subskala des KOOS zur Lebensqualität (KOOS QoL)

Short Form Health Survey (SF-36): has a total score and eight subscores. Scores are converted to a standardised 0 to 100 scale; see information above.

SF-36 zur Messung der Lebensqualität

Pain can be measured by different scores (PROMs):

Knee Injury and Osteoarthritis Outcome Score (KOOS): The KOOS has a subscale for pain (nine items) [74]; see information above.

Subskala des KOOS zum Schmerz (KOOS pain)

The Visual Analogue Scale (VAS) measures pain intensity using a 100-millimeter line scale. Patients mark their pain level along this line, where 0 represents “no pain” and 100 indicates “worst imaginable pain” or “pain as bad as it could be” at the other end. The MCID was reported as 18.6[83].

Visual Analogue Scale (VAS) – niedrige Punktzahl bedeutet weniger Schmerz

Western Ontario McMaster Universities Osteoarthritis Index (WOMAC): The WOMAC has a subscale for pain, including five items asking about pain at activity or rest [77]. The maximum value for pain is 50; see information above.

Subskala des WOMAC: WOMAC pain

Necessity of joint replacement:

The need for joint replacement surgery serves as a critical long-term outcome measure when evaluating treatments for chondral and osteochondral defects since the primary goal of these treatments is to prevent disease progression and avoid the necessity of joint replacement.

Notwendigkeit eines Gelenkersatzes

Structural repair:

Structural repair can be assessed with MRI interpretation (percentage of defect filling) and with the magnetic resonance observation of cartilage repair tissue (MOCART) score. Structural repair is considered a surrogate outcome, however according to preferences from clinicians the outcome was analysed and defined as critical. However, it should be interpretated with caution. It consists of 7 key variables: degree of defect repair and filling of the defect, integration to the border zone, surface of the repair tissue, structure of the repair tissue, signal intensity of the repair tissue, subchondral lamina, subchondral bone, adhesions, and synovitis. Each parameter is scored according to specific criteria, with higher scores indicating better outcomes [84]. The total score ranges from 0 to 100, where 100 represents optimal cartilage repair characteristics, and 0 indicates poor repair outcomes [85]. There is also an updated version of the MOCART available [86]; however, studies that were included used the original version.

strukturelle Wiederherstellung kann über die Interpretation der Magnetresonanztomographie (MRT) oder den MOCART Score evaluiert werden

4.1.2 Outcomes safety

The following outcomes were defined as *critical* to deriving a recommendation:

- Adverse events
- Serious adverse events

entscheidungsrelevante Sicherheitsendpunkte

Based on the European Commission guidelines [87] for medical devices the following definition was used for (serious) adverse events:

An adverse event refers to an untoward medical occurrence in a patient or clinical trial subject who has received a medicinal product. This event may occur during treatment, but it does not need to be directly caused by or related to the treatment itself. The event must have occurred while the patient was receiving the medicine, regardless of whether there is evidence of a causal relationship between the event and the treatment.

unerwünschte Ereignisse (UE)

A serious adverse event describes any unfavourable and unintended medical occurrence or effect at any dose of a medicinal product and results in one or more severe outcomes. These outcomes include death, situations that put the patient's life at risk, the need for initial or extended hospitalisation, lasting or significant disability or inability to function normally, or birth defects and congenital abnormalities. The severity of these events is determined by their outcomes rather than by the intensity of the medical occurrence itself.

schwere unerwünschte Ereignisse (SAE)

4.2 Included studies – effectiveness and safety

Overall, 10 studies (8 RCTs, 2 NRCTs), reported in a total of 13 publications [43-45, 49, 88-96], met our pre-defined inclusion criteria. The results are presented in two sections based on our PICOs. First, the outcomes of AMIC were examined compared to either MFx or ACI, followed by the analysis of AMIC+ (with BMAC) versus either AMIC, MACI or MFx. For the first PICO, three studies (five publications [43, 44, 88, 92, 93]) and the respective extraction data were used from a previous LBI-HTA report [37]. The table below gives an overview of the included publications and authors.

10 Studien (8 RCTs, 2 NRCTs) mit insgesamt 13 Publikation inkludiert

Table 4-1: Overview of included studies

Reference	Author	Year	Study Design	Comparison	Included in the Update 2019 [37]
AMIC					
[45]	Altschuler et al.	2024	RCT	MFx	No
[44] [88] [89]	Anders et al. Volz et al. Volz et al.	2013 2017 2024	RCT +FU publications	MFx	Yes Yes No
[49]	Fossum et al.	2019	RCT	ACI	No
[90]	Glasbrenner et al.	2020	RCT	MFx	No
[91]	Kim et al.	2020	RCT	MFx	No
[43]	Kon et al.	2018	RCT	MFx	Yes
[92] [93]	Stanish et al. Shive et al.	2013 2015	RCT + FU publication	MFx	Yes Yes
AMIC+					
[94]	De Girolamo et al.	2019	RCT	AMIC	No
[95]	Gobbi et al.	2015	NRCT	MACI	No
[96]	Gobbi et al.	2016	NRCT	MFx	No

Abbreviations: ACI … autologous chondrocyte implantation; AMIC … autologous matrix-induced chondrogenesis; AMIC+ … autologous matrix-induced chondrogenesis with bone marrow aspirate concentrate; MACI … matrix-induced autologous chondrocyte implantation; MFx … microfracture; NRCT … non-randomised controlled trial; RCT … randomised controlled trial

4.2.1 AMIC versus SoC

Seven RCTs, documented in 10 publications [43-45, 49, 88-93], were included in our review to compare AMIC versus standard of care (PICO 1). Six studies compared AMIC to MFx [43-45, 88-93], while one compared AMIC to ACI [49].

7 RCTs für AMIC vs. Standardtherapie

Study characteristics

The studies included 673 randomised patients: 390 in the intervention group (IG) and 283 in the control group (CG, 262 receiving microfracture and 21 receiving ACI). The proportion of female participants varied considerably, ranging from 11% to 73.3% in the IG and 23.1% to 79.6% in the CG. Patients were not blinded except in one study [90]. While surgeon blinding was not feasible due to the nature of the procedures, outcome assessors were blinded in six out of seven studies [43-45, 88-93].

390 Patient:innen in der Interventionsgruppe (IG) und 283 in der Kontrollgruppe (KG)

The surgical interventions across studies primarily involved mini-arthrotomy or arthroscopy procedures. In six of the seven studies, surgeons performed MFx and/or debridement before scaffold insertion [43, 44, 88-93]. Only one study [45] utilised a mini-open or open procedure without MFx. The studies employed various scaffold products, including an aragonite-based scaffold (Agili-c-implant) [45], Chondro-Gide® (Geistlich-Pharma AG) [44, 49, 88, 89], Chondrotissue® (BioTissue AG) [90], a porcine-derived collagen-augmented implant (CartiFill™) [91], MaioRegen™ (FinCeramica-Faenza) [43], and BST-CarGel® (Piramal Life Sciences) [92, 93]. Additionally, one study [44, 88, 89] separately analysed outcomes based on whether the scaffold was secured using glue or sutures.

OP: Mini-Arthrotomie oder Arthroskopie, meist kombiniert mit MFx

6 RCTs verglichen AMIC mit MFx, 1 RCT mit ACI

For six out of seven studies, the comparison was MFx alone, which was performed in an arthroscopy with special drills or awls [43-45, 88-93]. One study [49] compared AMIC to ACI, whereby chondrocytes were harvested first and cultivated for three to four weeks in the first step. In the second step, these cells were inserted under the sutured collagen patch.

Defektgrößen zwischen 0,5 und 9 cm² wurden eingeschlossen

The inclusion criteria among most studies were patients aged between 18 and 60 years presenting with cartilage defects in the knee. However, three studies [45, 90, 91] also included patients up to 75 [45], 68 [91] and 65 [91] years, respectively. Patients with ICRS grade 3a or above [44, 45, 88, 89], or with one or more defects with a lesion size between 0.5 to 9 cm^2, or without specifics concerning the lesion size [43, 49, 90-93] were included. Patients were excluded in cases of inflammation [43, 49, 90, 92, 93] or deeper defects than 8 mm [44, 45, 88, 89], for example.

KOOS, MRT-Evaluierung, VAS und IKDC als primäre Endpunkte

The primary endpoints included clinical evaluations through overall KOOS [45] at 24 months and change in KOOS score [49] at 24 months, MRI evaluation [44, 88, 89] after six, twelve, 24 and 60 months, defect filling [90, 92, 93] at twelve, 24 and 60 months, pain assessment using VAS [91] at 24 months, and the IKDC subjective score at 24 months [43]. For secondary endpoints, several studies examined KOOS total score [43, 49, 90], KOOS subscales [45, 49], and pain using VAS [43, 49, 89, 90]. Additional secondary measures included MRI results and defect filling [43, 45, 91], IKDC scores [43, 90, 91], and various other assessments: the mCKRS, ICRS and adverse events [44, 88, 89], treatment failure and Lysholm score[49], SF-36 [90], and the TAS [43]. One study [92] specifically aimed to demonstrate comparable clinical benefits between treatment groups at twelve months as a secondary endpoint.

Patient characteristics and follow-up

Alter zwischen 34 und 52 in beiden Gruppen

Participant demographics were generally well-matched between groups. The mean age ranged from 34 to 49 years in the IG and 35 to 52 years in the CG. Only one study [90] showed a significant age difference, with the IG being older (49.9 years, *range* 35-69, versus 36.7 years, *range* 18-51; $p=0.017$[11]). BMI was comparable between groups across all studies, ranging from 24.7 to 27.9 kg/m^2.

Defektgrößen variierten zwischen und innerhalb der Studien

Defect characteristics varied across studies. Concerning studies comparing AMIC with MFx, one study [90] reported a mean defect size of 1.7 cm^2 in both groups, while another study [45] documented defects larger than 3 cm^2 in 58.8% of intervention patients versus 48.8% of controls. In the remaining studies [43, 44, 88, 89, 91-93], mean defect size ranged from 2.3 to 4 cm^2 in the IG and 1.9 to 4.7 cm^2 in the CG. One study [91] reported a maximum lesion size of 9 cm^2 versus 12.8 cm^2. For the comparison AMIC versus ACI, the mean defect size was 5.2 cm^2 with a range of 2.0 to 12.3 cm^2 in the IG and 4.9 cm^2 with a range of 1.2 to 21.5 cm^2 in the CG.

klinische Klassifizierung mittels ICRS: Grad 3 und 4

Lokalisierung des Defekts häufig an den Femurkondylen

Clinical classification using the International Cartilage Repair Society (ICRS) scale was reported in four studies. One study [45] found ICRS grades III and IVa in 62.3% versus 81.0% of patients and grade IVb in 45.5% versus 64.3%. In two studies [49, 90], approximately 80% versus 70% of patients were ICRS grade III, while another study [91] reported ICRS grade IV in roughly 75% of patients across both groups. When reported, the femoral condyle was the predominant defect location, affecting approximately 70% of patients. Five studies [43-45, 49, 88, 89, 91] documented patients' surgical history prior to

[11] In this study, several baseline characteristics were statistically significant.

trial participation. Approximately 8% to 60% of patients had prior surgeries, with comparable numbers between groups within studies [43-45, 88-93]. One study [49] reported that 50% versus around 30% of included patients had two prior surgeries.

postoperative Rehabilitationsprogramme beinhalteten sukzessive Vollbelastung und Muskelaufbau im Zuge von Physiotherapie

Postoperative rehabilitation followed a structured, progressive protocol across all studies. Weight-bearing restrictions varied: Two studies [90, 92, 93] initially prohibited any weight-bearing, while other studies permitted partial weight-bearing immediately after surgery. The progression to full weight-bearing followed different timelines: Four studies [43, 45, 90, 91] allowed full weight-bearing at six weeks post-surgery; one study [44, 88, 89] implemented a gradual progression between seven to twelve weeks; and another study [92, 93] permitted full weight-bearing at eight weeks. All rehabilitation programs incorporated comprehensive physical therapy, including muscle strengthening exercises and joint mobilisation techniques, though specific protocols varied among studies.

Follow-up-Längen zwischen 24 und 120 Monaten

The studies exhibited varied follow-up durations. For the primary analysis, most studies [43, 45, 49, 90, 91] assessed the results at 24 months postoperatively (and before). One study [92, 93] had the primary analysis at 12 months postoperatively and the follow-up assessment after 60 months. One study additionally reported the results after 60 and 120 months [44, 88, 89]. Approximately 10% to 30% of patients were lost to follow-up.

Study characteristics and results of included studies are displayed in the Appendix Table A-2 and Table A-3, and in the evidence profile in Table A-8 and Table A-9.

4.2.2 AMIC+ versus SoC

AMIC+ vs AMIC (1 RCT), MACI (1 NRCT), MFx (1 NRCT)

One RCT and two NRCTs matched the criteria for the comparison of AMIC+ versus standard of care (PICO 2). The RCT compared AMIC+ to AMIC alone. The NRCTs investigated AMIC+ in comparison with MACI on the one hand and with MFx on the other.

Study characteristics

RCT (n=24), NRCTs (n=89)

The studies included a total of 24 patients in the RCT [94] and 89 in the NRCTs [95, 96]. In the RCT, patients were equally divided into the IG and the CG. In the NRCTs, 45 patients were assigned to the IG (18 receiving MACI, 27 receiving MFx) and 44 to the CG (19 comparing to MACI, 25 comparing to MFx).

geringerer Frauenanteil in allen Gruppen

The proportion of female participants was 33.3% in IG and 41.7% in CG in the RCT. Among the NRCTs, the proportion ranged from 36.0% to 44.4% in the IG and from 36.0% to 52.6% in the CG. None of the studies implemented patient blinding. Given the nature of the intervention, blinding surgeons was not feasible. However, outcome assessors were blinded in the RCT and one NRCT, while in the other NRCT [96], no blinding was applied.

keine Patient:innenverblindung

OP: minimalinvasive Arthrotomie + MFx

All studies employed a surgical intervention approach involving minimally invasive arthrotomy and MFx. All studies harvested bone marrow from the ipsilateral iliac crest. In the RCT, 24 mL of bone marrow was mixed with 6 mL of Anticoagulant Citrate Dextrose Solution A, whereas the NRCTs used 60 mL of bone marrow exclusively. As a scaffold, the RCT employed a collagen type I/III bilayer matrix (Chondro-Gide®, Geistlich Pharma AG [94]), while the NRCT

Knochenmark vom Beckenkamm

utilised a non-seeded 3-dimensional scaffold (HYAFF11, Hyalofast®, Anika Therapeutics, Srl, Abano Terme, Italy) [95] and a 3-dimensional hyaluronic acid-based scaffold (Hyalofast®; Anika Therapeutics Srl) [96]. Fibrin glue was used as the primary method for securing the scaffold (RCT) and/or supplemented with a polydioxanone suture (NRCTs).

Matrizen: Chondro-Gide®, HYAFF1, Hyalofast

The comparators differed between the studies. The standard AMIC, which performs AMIC equal to the intervention but without adding BMAC, was used in the RCT. One NRCT [95] compared, a two-step surgery that harvests biopsies from the knee and expands autologous chondrocytes in vitro and seeds them onto a scaffold that is implanted in a second surgery. The final comparator was MFx alone [96], in which holes are drilled in the subchondral plate to release bone marrow.

Komparatoren: AMIC, MACI, MFx

Inclusion criteria were mainly defined by age (18-55 years in RCT; 30-60 years in NRCTs), lesion grade (III or IV in RCT; IV in NRCTs), lesion size 2-8 cm^2 (RCT) and BMI 20-30 kg/m^2 (NRCTs). In all trials, the major exclusion criteria were various other pathologies.

Einschlusskriterien

The primary endpoint of the RCT was the VAS and Lysholm score up to 100 months postoperatively to assess pain and knee function. In addition, the function was assessed as a secondary endpoint up to 24 months follow-up using the TAS and IKDC objective, which were finally replaced by the KOOS subscales at 60 and 100 months follow-up. Structural repair was also assessed as a secondary endpoint using MRI for up to 24 months. The NRCTs assessed their primary endpoints after 24 months and final (~60 months on average) follow-up, with the assessment of function incorporating the IKDC objective and subjective as well as the TAS. Furthermore, one NRCT assessed pain with the VAS and structural repair with radiographs and MRI [95], while the other NRCT additionally assessed the Lysholm score to measure function as the primary endpoint [96]. Only one NRCT incorporated the following outcome measures as secondary endpoints: IKDC, KOOS, TAS, and Lysholm, categorised by age, lesion size, and lesion count at 60-month follow-up.

primäre Endpunkte RCT: VAS, Lysholm

primäre Endpunkte NRCT: IKDC objective/subjective, TAS (2 NRCTs) + VAS, Röntgenbilder, MRT (1 NRCT), Lysholm (1 NRCT)

Patient characteristics and follow-up

Demographic data at baseline were homogeneous between the two groups in the RCT, and differences within the NRCTs were not significant, except for age (47.0 ±7.0 vs. 42.9 ±7.7, $p=0.035$) in one study [96]. The mean age differed between 30 years (±11.3 vs. ±10.2) in both RCT groups and 45.5 to 47.0 years in the IG and 43.1 to 42.9 years in the CG of the NRCTs. BMI was comparable in one NRCT, while the other provided no data. The RCT reported on weight instead of BMI, which was also comparable.

homogene demografische Daten, Ausnahme Alter in 1 NRCT

Defect size differed between studies. The RCT reported homogenous values between both groups (*mean ±SD, cm^2:* 3.4 ±0.8 vs. 3.8 ±1.0). Also, the difference in average lesion size between IG and CG of one NRCT [95] was not significant (*cm^2/lesion:* 5.45 vs. 7.12, $p=0.174$), whereas statistical significance was reported for the other (median [IQR], *cm^2;* 6.5 [6.3] vs. 4.5 [1.5], $p=0.003$) [96].

variierende Defektgröße

The location of the defect was observed to be femoral condyle in one RCT and one NRCT [96] pre-dominantly, while in one NRCT patellofemoral was the only location of inclusion. Patients in the RCT had prior surgery, with 25% of the IG and 50% of the CG having undergone the procedure (p=not statistically significant). The NRCTs did not report data.

Lokalisierung: v. a. Oberschenkelkondylen

All patients underwent a staged rehabilitation protocol that included, in particular, weight-bearing restriction (1 RCT, 1 NRCT [96]), maintenance of range of motion (1 RCT, 1 NRCT [96]), and moreover, initiation of active functional training, for example (1 NRCT [96]). One NRCT [95] did not contain any details.

mehrstufiges Rehabilitationsprotokoll

The studies differed in follow-up duration of primary analysis, ranging from an average of 54.7 months (IG) and 59.7 months (CG) in one NRCT [95] and 60 months in another NRCT [95], up to 100 months in the RCT. In total, the RCT experienced a loss of approximately 33.3% of patients due to follow-up, while approximately 1.6% of patients were lost to follow-up from NRCTs.

Follow-up-Länge von ~54.7 bis 100 Monate

Study characteristics and results of included studies are displayed in the Appendix Table A-4 and A-5, and in the evidence profile in Table A-10 and A-12.

4.3 Included studies – clinical results

First, the results of the comparison AMIC with standard of care (AMIC vs. MFx, AMIC vs. ACI) are reported, followed by the comparison AMIC+ with the standard of care (AMIC+ vs. AMIC, AMIC+ vs. MACI, AMIC with BMAC vs. MFx).

Berichterstattung zuerst für AMIC gefolgt von AMIC+

4.3.1 AMIC versus SoC

AMIC versus MFx

Six RCTs [43-45, 88-93], including 632 investigated AMIC versus MFx. Outcomes were reported in most studies up to 24 months. Two studies reported follow-ups at 60 months [93] and one at 120 months [89].

6 RCTs verglichen AMIC mit MFx, Follow-up 24-120 Monate

Effectiveness[12]

Morbidity was assessed with the subscale KOOS pain, VAS, and WOMAC pain as patient-reported outcome measures (PROMs) and structural repair as clinical outcome measures (CROMs).

Morbidität: KOOS pain, VAS, WOMAC pain

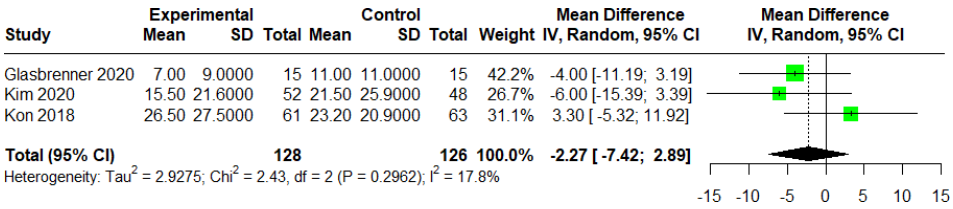
The **KOOS pain** was reported in four out of six studies (n=505) at 24 months follow-up [43, 45, 90, 91]. Statistically significant differences were not found in the included studies. One study found mean scores of 89.5 in the IG compared to 69.1 in the CG, whereby higher scores indicate less pain [45, 90, 91]. Another study reported median scores of 90.3 (with an interquartile range of 82.5 to 95.2) in the IG compared to 91.8 (with an interquartile range of 83.3 to 99.9) in the CG [45]. The third study showed mean scores of 82.2 ±11.6 in the IG versus 77.8 ±16.1 in the CG. This difference was not statistically significant (p=0.3317), with a mean difference of 4.4 (95% confidence interval ranging from -1.2 to 9.9) [90]. The fourth study reported mean scores of 77.6 versus 79.4, with mean changes from baseline of 18.2 versus 21.9 respectively [91].

KOOS pain zeigte keine stat. signifikanten Unterschiede zwischen den Gruppen

The **VAS** was reported in four [43, 89-91] out of six studies (n=301). The pooled mean difference between groups at 24 months was not statistically significant (-2.27; 95%CI: -7.42 to 2.89; I^2=17.8%, Figure 4-1).

gepoolte Mittelwertdifferenz (MD, 3 Studien) zeigt keine stat. signifikanten Unterschiede zwischen den Gruppen nach 24 Monaten

[12] This section addresses the assessment elements provided in Table A-18



Abbreviations: CI … confidence interval; IV – inverse variance; SD … standard deviation
Note: lower scores indicate less pain

Figure 4-1: AMIC versus MFx – pain measured with the VAS score

Furthermore, one study [89] reported long-term outcomes at 60 and 120 months. At 60 months, the mean scores were 11 ±20 and 15 ±22 for the two IGs (AMIC glued and AMIC sutured, respectively), compared to 30 ±19 for the CG. At 120 months, the mean scores were 12 ±21 and 11 ±16 for the IGs, compared to 31 ±20 for the CG.

WOMAC pain (1 Studie); keine stat. signifikanten Unterschiede

The **WOMAC pain** subscale was reported in one study [92, 93] out of six at 12 and 60 months follow-up (n=80). No statistically significant difference between study groups could be found. At 12 months, the mean change was -16.2 ±1.2 in the IG and -16.9 ±1.2 in the CG, with a mean difference of 0.7 (95%CI: -2.6 to 4.0). At 60 months, the mean change was -15.4 ±1.5 in the IG and -16.6 ±1.2 in the CG (p=0.474), with a mean difference of 2.9 (95%CI: -1.5 to 7.2).

Kniegelenkersatz in 5,9 % in der AMIC-Gruppe

The necessity of joint replacement was reported in one out of seven studies (n=47). At 60 months of follow-up, one total joint replacement (5.9%) was necessary for the AMIC glued group.

strukturelle Wiederherstellung (6 Studien): 3 Studien zeigten stat. signifikant bessere Ergebnisse in der AMIC-Gruppe (z. B. 85,5 % vs. 30,9 % erreichten ≥75 % Defektfüllung)

Structural repair was assessed in six [43-45, 88-93] studies (n=632) through the evaluation of defect filling at 12, 24, and 60 months. While the MOCART score was commonly used, total scores were only reported in two studies [44, 88, 89, 91]. Three studies demonstrated statistically significant differences in defect filling (n=431). One study [45] found that 85.5% of patients in the IG achieved ≥75% defect filling compared to 30.9% in the CG at 24 months (p<0.0001). Another study [91] found significantly fewer patients in the IG with less than 50% defect filling compared to the CG (6.1% vs. 17.1%, p= 0.0377) at 24 months. The third study [92, 93] reported significantly better defect filling in the IG at 12 months with mean percentages of 92.8 ±2.0 versus 85.2 ±2.1 (p=0.011), and at 60 months with 93.79 ±1.16 versus 86.96 ±2.85 (p=0.017).

3 Studien: keine stat. signifikanten Ergebnisse

In studies showing no statistically significant differences, one study [44, 88] reported that at least 60% of IG patients achieved more than two-thirds filling, compared to 25% in the CG. At 60 months, the CG showed the lowest defect filling compared to both IGs (glued and sutured scaffold). Another study [90] found more than 50% defect filling in both groups at 24 months, while one study [43] observed defect filling of 49.0% versus 65.9% at 24 months.

MOCART Score in 2 Studien berichtet (stat. nicht signifikant)

Regarding MOCART scores, no statistically significant differences were found in total scores between groups. Only one study [91] reported significant differences in the subscale 'degree of defect repair and filling of the defect' with mean scores of 12.1 ±5.4 versus 9.6 ±5.2 (p=0.0201). Another study [89] reported MOCART total scores at 120 months of 34.4 ±23.2 and 31.0 ±20.3 versus 37.7 ±29.3 (p=0.879).

Function was assessed with the KOOS total scores or subscales (Symptoms, ADLs and sport/rec), IKDC subjective, TAS, the mCKRS, the ICRS, WOMAC and the SF-36 as PROMs.

Funktion: u. a. mit patient:innenberichteten Tests evaluiert

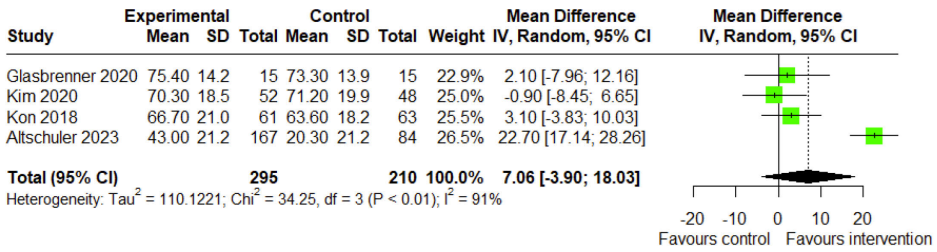
The **KOOS** was used in four [43, 45, 90, 91] out of six studies and reported at baseline and 24-month follow-up (n=546). Two studies reported the total KOOS scores and the other two studies reported the subscales. One study [45] out of seven (n=251) demonstrated statistically significant mean differences between groups at 24 months (22.5 [95%CI: 17.0-28.0], $p<0.0001$) in favour of the IG. The other study [91] showed mean scores at 24 months of 77.1 ±14.1 in the IG versus 75.2 ±15.5 in the CG ($p=0.6906$), without statistical significance. Considering the studies reporting the subscales, one study [90] could not find any statistically significant differences between groups at 24 months (*median [IQR]*: KOOS symptoms: 85.7 [79.6-88.7] vs. 89.5 [85.5-93.3], KOOS ADLs: 95.0 [89.3-96.8] vs. 99.3 [96.0-99.9], KOOS Sport/rec: 92.5 [75.3-92.5] vs. 85.0 [54.9-100.0]). Another study [43] showed increases in subscales for both groups but found no statistically significant differences between the groups.

KOOS (4 Studien): stat. signifikante Ergebnisse in 1 Studie (MD: 22.5)

The **IKDC** was reported in four [43, 45, 90, 91] studies out of six (n=505). The pooled mean difference between groups at 24 months follow-up was 7.06 (95%CI: -3.90 to 18.03) with high heterogeneity ($I^2=91.2\%$, see Figure 4-2). One study [45] demonstrated statistically significant differences between groups after 24 months, with a mean difference of 22.7 (95%CI: 16.8-28.6, $p<0.001$) in favour of the IG. Another study [43] reported changes after 24 months of 23.5 versus 22.5 without statistical significance. The other two studies [90, 91] did not report mean differences. At 24-month follow-up, scores showed no statistically significant differences between groups: 75.4 ±14.2 versus 73.3 ±13.9 [90], and 70.3 ±18.5 versus 71.2 ±19.9 ($p=0.6281$)[91].

IKDC (4 Studien) gepoolte MD zeigt keine stat. signifikanten Ergebnisse

1 Studie erreichte stat. signifikante Ergebnisse (MD 22.7)



Abbreviations: CI … confidence interval; SD … standard deviation
Note: higher scores indicate better function

Figure 4-2: AMIC versus MFx – subjective International Knee Documentation Committee (IKDC) score

The **WOMAC** (subscales stiffness and physical function) was reported in one [92, 93] out of six studies (n=80). Changes were not statistically significant at both time points: at 12 months -55.9 ±4.24 in the IG versus -60.6 ±4.4 in the CG ($p=0.4439$), and at 60 months -56.5 ±4.6 versus -62.1 ±3.4 ($p=0.326$).

WOMAC (1 Studie): keine stat. signifikanten Unterschiede

The **TAS** was reported in one [43] out of six studies (n=124). No statistically significant changes were found between groups from baseline to 24-month follow-up, with average improvements of 4.0 (range 1.0-9.0) and 4.0 (range 2.0-8.0), respectively.

TAS (1 Studie): keine stat. signifikanten Unterschiede

The **ICRS** was reported in one [44] out of six studies (n=47). Group data was only available after 12 months, showing scores of 15 ±13 and 16 ±15 versus 15 ±17, with changes after 12 months of -31.0, -38.0 versus -42.0. Results were not statistically significant between groups.

ICRS (1 Studie): keine stat. signifikanten Unterschiede

The **mCKRS** was reported in one [44, 88, 89] out of six studies (n=47) comparing AMIC with MFx reported the mCKRS, whereby higher scores indicate better function. At 24 months follow-up, scores were 85 ±18 for AMIC glued versus 74 ±26 for the MFx group, with changes of +37 versus +36. At 120 months follow-up, statistically significant differences were observed (84.3 ±17.1 and 81.6 ±21.2 vs. 56.1 ±18.6, $p<0.05$).

mCKRS (1 Studie): stat. signifikante Unterschiede nach 120 Monaten zugunsten AMIC

The **SF-36** (subscale physical functioning) was reported in two [90, 92, 93] out of six studies (n=110). One study [90] described narratively that no statistically significant differences between groups were found. The other study [92, 93] reported changes at both follow-up points without statistically significant differences (12 months: +13.0 ±1.5 vs. +14.8 ±1.5, $p=0.416$; 60 months: +13.1 ±1.6 vs. +14.5 ±1.4, $p=0.478$).

SF-36 (2 Studien): keine stat. signifikanten Unterschiede

Health-related quality of life was assessed using the KOOS subscale QoL and the SF-36.

KOOS QoL was reported in three [43, 45, 90] out of six studies (n=405) at 24 months follow-up. One study [45] reported scores of 73.9 versus 48.8, with a posterior probability of superiority of 1.00, exceeding the prespecified Bayesian posterior probability. Two studies [43, 90] found no statistically significant differences at 24 months (median [IQR, 95%CI]: 62.4 [48.6-71.9; 24.5-99.8] vs. 68.8 [49.9-81.1; 24.5-99.8]; 54.1 vs. 55.3).

KOOS QoL (3 Studien): 1 Studie zeigte stat. signifikante Verbesserung der QoL nach AMIC

The **SF-36** was reported in two [90, 92, 93] out of six studies (n=110) at 12 and 60 months follow-up [92, 93] or 24 months [90]. No statistically significant differences were found between study groups in both studies. One study [90] did not report values, while the other [92, 93] reported changes after 12 months (+3.5 ±1.7 vs. +0.8 ±1.6, $p=0.229$, MD 2.7 [95%CI: -1.9 to 7.3]) and after 60 months (+2.7 ±1.3 vs. -0.17 ±1.8, $p=0.125$, MD 2.9 [95%CI: -1.5 to 7.2]).

SF-36 (2 Studien): keine stat. signifikanten Unterschiede

Safety[13]

Patients' safety was evaluated through the *clinical outcomes*: adverse events, serious adverse events, procedure-related adverse events, device-related adverse events, and re-operation rate.

Sicherheit: UE und SUE

Adverse events were reported in five [43-45, 88-90, 92, 93] out of six studies (n=532). One study [44, 88, 89] reported 13 adverse events in nine patients over 120 months. Another study [43] reported overall adverse events up to 24 months in 21% of the IG versus 6.5% of the CG. One study [45] found that more than one adverse event occurred in 58.7% versus 77.4% of patients after 24 months, including increased transient knee pain following surgery (15.0% vs. 39.3%) and increased swelling or effusion (5.4% vs. 4.8%). Another study [90] reported adverse events up to 24 months: severe effusion[14] (0.0% vs. 8.3%), mild swelling (25.0% vs. 0.0%), restricted range of motion (16.7% versus 0.0%), and allergic reactions (0.0% vs. 0.0%). One study [92, 93] reported adverse events in 98% versus 92% after 12 months, and 19.0% versus 27.0% after 60 months, also reporting nausea after surgery.

UE (5 Studien): vergleichbares Auftreten von UE in den Studien

[13] This section addresses the assessment elements provided in Table A-19.

[14] According to the study [90] this was not considered a serious adverse event.

Serious adverse events were reported in six studies [43-45, 88-93] including 632 patients. One study [44, 88, 89] reported no serious adverse events up to 120 months. Another study [45] reported one or more serious adverse events in 15.6% versus 20.2% of patients until 24 months, including wound complications requiring antibiotics (1.2% vs. 1.2%), septic arthritis requiring implant removal (0.6% in the IG), decreased range of motion (1.2% in the IG), persistent muscle atrophy (4.8% in the CG), and deep venous thrombosis (0.6% vs. 1.2%). One study [90] reported serious adverse events in 8.3% of patients in both groups. Another study [91] reported serious adverse events in 4.4% versus 4.6% of patients, including urethral caruncle (IG, 2.2%), acute hepatoma (IG, 2.2%), knee pain and swelling (CG, 2.3%), and metal removal (CG, 2.3%). One study [42] reported serious adverse events in 4.8% versus 1.6% of patients. Another study [92, 93] reported serious adverse events in 12.2% versus 2.7% after 12 months and 0.0% versus 3.8% after 60 months.

SUE (6 Studien): Studien berichten weniger oder gleich viele SUEs nach AMIC verglichen mit MFx

Procedure-related adverse events were reported in five [43-45, 88, 89, 91-93] out of six studies (n=602). No statistically significant differences between groups were observed. Two studies [44, 88, 89, 91] reported no procedure-related adverse events. Two studies reported procedure-related adverse events until 24 months follow-up in 13.8% versus 27.4% [45] or 12.9% versus 4.8% [43] of patients. Another study [92, 93] reported procedure-related adverse events in 93% versus 77% after 12 months and 6% versus 8% after 60 months.

eingriffsbezogene UE (4 Studien): keine stat. signifikanten Unterschiede

Device-related adverse events were reported in two [43, 92, 93] out of six studies (n=331). One study [45] reported these events in 5 IG patients (3%). The other study [92, 93] reported device-related adverse events in the IG in 22% after 12 months and 6% after 60 months.

implantationsbezogene UE (2 Studien): 3 bis 22 % der Patient:innen

Re-operation rate[15] was reported in six studies [44, 45, 88, 89], including 532 patients. One study [45] reported no revision surgeries in the IG compared to four cases (4.8%) in the CG, with significantly fewer treatment failures in the IG (7.2% versus 21.4%, $p=0.002$). Another study [44] observed 5.0% versus 15.4% at 24 months. One study [90] noted identical failure rates in both groups (8.3%), while another study [43] noted 3.2% vs. 0% failure rates. Another study [92, 93] reported no failures were reported in the IG compared to one case (3.8%) in the CG at 60 months follow-up.

Re-Operation (6 Studien): 1 Studie zeigte stat. signifikant weniger Re-Operationen nach AMIC

AMIC versus ACI

One RCT [49] (n=41) was included for the comparison of AMIC with ACI, reporting results for a follow-up until 24 months after surgery.

AMIC versus ACI: 1 RCT, 24 Monate Follow-up

Effectiveness[16]

Morbidity was assessed with the PROMs KOOS pain and the VAS.

Morbidität: KOOS pain und VAS

The **KOOS pain** was reported in the included study [49] (n=41) at 24 months follow-up. The study did not find statistically significant differences between groups (values not provided).

KOOS pain: keine stat. signifikanten Unterschiede

For the **VAS**, no significant differences between groups were detected. The mean scores were 27.0 (95%CI: 17.1-37.0) in the IG versus 30.4 (95%CI: 20.1-41.2) in the CG, with a mean delta at 24 months of 30.6 versus 19.6 ($p=0.19$) [49].

auch keine stat. signifikanten Unterschiede in der VAS

[15] Re-operation rate was also referred to as (treatment) failure [45, 91].

[16] This section addresses the assessment elements provided in Table A-18.

The included study [49] did not report the necessity of joint replacement and structural repair.

Notwendigkeit für Knieersatz nicht berichtet

Function was assessed with the KOOS and Lysholm Score as PROMs.

Funktion KOOS und Lysholm Score

The **total KOOS** was reported in the included study [49] (n=41). No statistically significant differences between groups were found at 24 months (mean delta between groups: 18.1 versus 10.3, $p=0.17$).

keine stat. signifikanten Unterschiede beim KOOS

The mean delta between groups for the **Lysholm Score** was 17.0 versus 19.7 ($p=0.66$), and the mean was 70.1 (95%CI 61.0-79.6) versus 69.6 (95%CI 62.2-76.9) [49].

auch kein Unterschied beim Lysholm Score

Health-related quality of life was not assessed in the included study [49].

HRQoL nicht berichtet

Safety[17]

Patients' safety was evaluated through the *clinical outcomes*: serious adverse events and re-operation rate.

Sicherheit

No **serious adverse events** occurred in the included study [49] (n=41) until 24 months follow-up.

keine SUE

Re-operation rate was reported in the included study [49] (n=41). Comparable rates of re-arthroscopy (14.3% vs. 15.0%) and re-operations (4.8% vs. 5.0%) were observed until the 24-month follow-up.

Re-Operationen: 4.8 % vs. 5.0 % nach 24 Monaten

The included study [49]did not report adverse, procedure, or device-related adverse events.

andere Sicherheitsendpunkte nicht berichtet

4.3.2 AMIC+ versus SoC

AMIC+ vs. AMIC

One RCT [94] (n=24) investigated AMIC+ (n=12) compared to the standard AMIC procedure (n=12). In the ≤24-month period, data were collected at the 6-, 12- and 24-month marks. For patients with a duration of treatment beyond 24 months, the 60- and 100-month follow-ups were measured. At these subsequent follow-ups, the IKDC was replaced by the KOOS Score, as patients were interviewed via telephone. Consequently, no baseline data for the KOOS subscales is reported.

1 RCT: 6, 12, 24, 60, 100 Monate Follow-up

Effectiveness[18]

Morbidity was assessed with the subscale KOOS pain and VAS as patient-reported outcome measures (*PROM*) and structural repair as clinician-reported outcome measures (CROM).

Morbidität: KOOS pain, VAS, strukturelle Wiederherstellung

The **KOOS pain** subscale did not demonstrate statistical significance in the comparison of study groups at either the 60-month or the 100-month follow-up (*mean [max.]:* 65.9 [86.7] vs. 62.6 [79.4]; 61.5 [84.2] vs. 62.5 [79.4]).
No statistically significant group differences[19] were calculated for the **VAS** at any time point.

KOOS pain + VAS nicht stat. signifikant

[17] This section addresses the assessment elements provided in Table A-19.

[18] This section addresses the assessment elements provided in Table A-18.

[19] Self-calculated mean differences based on the reported values of improvement within time.

The included study did not report the necessity of joint replacement.

Gelenkersatz nicht berichtet

In terms of **structural repair**, a similar defect size and filling in the two groups was reported, as well as an MRI with a 30% reduction in bone marrow lesion in the entire cohort at 24 months.

strukturelle Wiederherstellung vergleichbar

Function was assessed using the KOOS subscales Symptoms, ADLs, and Sport/rec, as well as the TAS and the Lysholm score as *PROMs* and the IKDC objective as *CROM*.

Funktion: KOOS Subskalen, TAS, Lysholm, IKDC objective

For the **KOOS** symptoms, no statistical analysis between groups was calculated at 60- (*mean [max.]:* 76.1 [86.0] vs. 67.0 [90.4]) and 100-month follow-up (*mean [max.]:* 76.1 [86.0] vs. 67.0 [90.4]).

KOOS nicht stat. signifikant

The **KOOS ADLs** and **Sport/rec**, which exhibit higher scores corresponding to superior function, demonstrated no significant findings at all time points (*scale, months=mean [max.]: ADLs 60 months*=83,8 [88,2] vs. 82.7 [87.4]; *ADLs 100 months*=78.7 [89.6] vs. 74.0 [87.9]; *Sport/rec 60 months*=62.2 [84.9] vs. 49.4 [83.8]; *Sport/rec 100 months*=29.7 [84.8] vs. 41.9 [87.2]).

The **TAS** indicates a higher activity level if a higher score is achieved. However, no significant group difference[19] was detected at any time point (*months= MD [95% CI]: 24 months*=-0.9 [95% CI: -2.6;0.8]; *60 months*=-0.6 [95% CI: -2.1;0.9]; *100 months*=-0.2 [95% CI: -1.9;1.5]).

Higher **Lysholm score** values are associated with better knee function and fewer symptoms but are not statistically significant at any point in time (*months=MD [95% CI]: 24 months*=3.0 [95% CI: -0.2;6.2]; *60 months*=3.1 [95% CI: -3.7;9.9]; *100 months*=3.5 [95% CI: -2.8;9.8]).

Lysholm Score nicht stat. signifikant

The **IKDC objective**, categorised as A=normal, B=nearly normal, C=abnormal, D=severely abnormal, demonstrated a significant increase in A compared to pre-op (p <0.05). Furthermore, A exhibited a higher percentage of patients than B, C and D in the IG, while no significant difference was observed in the CG at 24 months follow-up. Statistical analysis of group differences was not reported.

IKDC objective stat. Analyse nicht berichtet

Health-related quality of life was assessed by the **KOOS subscale QoL** (*PROM*), which improves with increasing scores. However, its evidence of group difference was not taken into account (*months=mean [max.]: 60 months*=57.4 [91.1] vs. 52.3 [87.4]; *100 months*=37.9 [77.1] vs. 18.6 [57.8]).

KOOS QoL nicht stat. signifikant

Safety[20]

Patients' safety was evaluated through clinical outcomes, such as adverse events and re-operation rate. A single instance of arthrosynovitis was documented as an adverse event in the CG of 12 patients. No patient required additional surgical intervention.

1 UE in KG

AMIC+ vs. MACI

One NRCT [95] (n=37) investigated AMIC+ (n=18) compared to MACI (n=19) at 24 months and a final follow-up (~ 60 months). The minimum follow-up period for the final follow-up was 36 months, with an average of 54.16 months in the IG and 59.69 months in the CG. All evaluated scores significantly improved at 2-year and final follow-up (all patients), compared to preoperative scores (p=0.001). Difference in improvement between the two groups was determined for the final follow-up only.

1 NRCT: 24 Monate und finales (~60 Monate) Follow-up

[20] This section addresses the assessment elements provided in Table A-19.

Effectiveness[21]

Morbidity was assessed with the subscale **KOOS pain**, **VAS** as PROMs, and **structural repair** as *CROM*.

Morbidität: KOOS pain, VAS, strukturelle Wiederherstellung

The **KOOS pain** score (*mean ±SD:* 93.50 ±8.22 vs. 80.73 ±11.79, $p=0.336$) and the **VAS score** (*mean ±SD:* 0.33 ±0.68 vs. 0.84 ±0.68, $p=0.418$) resulted in no statistically significant difference in improvement between the two groups at final follow-up. At 24 months follow-up group differences were neither reported for KOOS pain (*mean ±SD:* 90.33 ±10.15 vs. 83.26 ±10.59) nor for VAS (*mean ±SD:* 0.72 ±1.01 vs. 0.47 ±0.61).

KOOS pain + VAS nicht stat. signifikant

Concerning **structural repair**, MRI showed complete or near complete (>50%) defect filling in 81% of IG and 76% of CG and complete integration with adjacent cartilage in 93.7% of IG and 88.2% of CG, though no statistical significance. In addition, there was no evidence of hypertrophy in either group, two cases of subchondral oedema in each group, and no cysts or sclerosis of the subchondral bone in either group.

strukturelle Wiederherstellung nicht stat. signifikant

Function was assessed with the **KOOS subscales Symptoms**, **ADLs** and **Sport/rec**, as well as the **TAS** and IKDC subjective as *PROMs* and the **IKDC objective** as *CROM*.

Funktion: KOOS Subskalen, TAS, Lysholm, IKDC subjective/objective

The **KOOS subscales** did not show statistically significant differences in improvement between the two groups for symptoms (*mean ±SD:* 90.61 ±10.85 vs. 81.05 ±11.04, $p=0.430$), **ADLs** (*mean ±SD:* 90.61 ±10.85 vs. 81.05 ±11.04, $p=0.430$) or **Sport/rec** (*mean ±SD:* 79.72 ±17.37 vs. 68.84 ±15.25, $p=0.173$) at the final follow-up. At 24 months group differences were not calculated (*score=mean ±SD:* symptoms=84.94 ±11.92 vs. 86.05 ±9.47; ADLs=88.67 ±10.90 vs. 85.94 ±13.66, Sport/rec=68.78 ±23.36 vs. 71.42 ±14.16).

KOOS nicht stat. signifikant

The **TAS** also revealed no statistically significant group differences in the improvement observed at the final FU (*mean ±SD:* 6.05 ±1.10 vs. 5.26 ±1.14, $p=0.220$). Group differences were not calculated for 24 months of follow-up.

TAS nicht stat. signifikant

A statistically significant difference between the two groups was found for the **IKDC subjective** at the final follow-up in favour of the IG, with a better knee function (*mean ±SD:* 82.52 ±10.72 vs. 75.70 ±9.85, $p=0.015$).

IKDC subjective stat. signifikant zugunsten AMIC+ (finales Follow-up)

In the final follow-up of the **IKDC objective**, 14 out of 18 patients in the IG were categorised as normal (A) and four as nearly normal (B). In the CG, ten out of 19 patients were categorised as normal (A), eight as nearly normal (B), and one as abnormal (C). However, the group difference was not statistically significant ($p=0.12$).

IKDC objective stat. nicht signifikant

Health-related quality of life was assessed by the **KOOS subscale QoL** (*PROMs*). At the final follow-up, the IG demonstrated a superior QoL in comparison to the CG; however, the disparity between the two groups did not attain statistical significance (*mean ±SD:* 84.00 ±14.81 vs. 76.10 ±16.90, $p=0.107$).

KOOS QoL nicht stat. signifikant

[21] This section addresses the assessment elements provided in Table A-18.

Safety[22]

Patients' safety was evaluated through *CROMs*: adverse events and re-operation rate. No adverse reactions or postoperative infections were noted in any of the patients. In both groups, one case of debridement and mobilisation (intraarticular adhesions) was reported at seven and six months postoperatively was reported.

kein UE in beiden Gruppen

AMIC+ vs. MFx

One NRCT [96], including 52 patients, investigated AMIC+ (n=27) compared to MFx (n=25) at 24- and 60-months follow-up. The outcomes were evaluated using the median and interquartile range (IQR), which were determined through calculation of the difference between the first and third quartiles. The KOOS Score was only available after five years follow-up because of the recent validation of this tool for the language of the study (Italian).

1 NRCT: 24 + 60 Monate Follow-up

Effectiveness[23]

Morbidity was assessed using the subscale **KOOS pain** as *PROM*. Other measurements, such as the VAS or the MOCART, to capture structural repair were not reported.

Morbidität: KOOS pain, VAS NR

The **KOOS pain** scale revealed a statistically significant difference between the two groups under investigation, in favour of IG (*median [IQR]:* 95 [10] vs. 87 [31], $p=0.023$), indicating a lower level of pain in the AMIC+ group.
VAS Score was not reported.

KOOS pain nicht stat. signifikant

Function was assessed with the **KOOS subscales Symptoms, ADLs and Sport/rec**, as well as the **IKDC subjective, TAS** and the **Lysholm score** as *PROM* and the **IKDC objective** as *CROM*.

Funktion: KOOS Subskalen, TAS, Lysholm, IKDC subjective/objective

KOOS Symptoms and **KOOS ADLs** did not show statistical differences between IG and CG at 60 months (*median [IQR]:* 90 [12] vs. 87 [23], $p=0.060$; and 95 [20] vs. 95 [23], $p=0.217$), the only time point reported. However, KOOS Sport/rec revealed that IG demonstrated statistically better function in comparison to CG (*median [IQR]:* 85 [17] vs. 68 [37], $p=0.013$).

KOOS Symptoms + ADL nicht stat. signifikant; KOOS Sport/rec stat. signifikant nach Monat 60 zugunsten AMIC+

The **TAS** revealed no substantial disparities between the IG and CG groups at the baseline (*median [IQR]:* 2 [2] vs. 3 [1], $p=0.077$) or the 24-month mark (*median [IQR]:* 5 [1] vs. 5 [2], $p=0.115$). However, a significant difference was observed at the 60-month follow-up. At this time point, IG demonstrated higher scores in comparison to CG, indicating enhanced ADL (*median [IQR]:* 6 [1.5] vs. 4 [2], $p<0.001$).

TAS stat. signifikant nach Monat 60 zugunsten AMIC+

Regarding the **Lysholm Score**, the difference between the two investigation groups was not statistically significant at any time point. IG scores were higher than CG scores at baseline and at 24- and 60-months follow-up (time point=*median [IQR]:* baseline=45 [10] vs. 45 [25], $p=0.815$; 24 months=90 [25] vs. 90 [12], $p=0.845$; 60 months=90 [17] vs. 80 [20], $p=0.178$).

Lysholm nicht stat. signifikant

The **IKDC subjective** also showed no statistically significant group differences at any time (*time point=median [IQR]: Baseline*=40 [29] vs. 42 [24], $p=0.143$; *24 months*=83 [15] vs. 80 [25], $p<0.763$; *60 months*=86 [14] vs. 77 [26], $p=0.086$).

IKDC subjective nicht stat. signifikant

[22] This section addresses the assessment elements provided in Table A-19.

[23] This section addresses the assessment elements provided in Table A-18.

According to the **IKDC objective** score (*A*=normal/*B*=nearly normal/*C*=abnormal/*D*=severely abnormal) a significantly greater proportion of patients in IG, compared with CG, were classified as normal or nearly normal at 24- (*A/B/C/D:* 16/9/0/0 vs 4/12/9/0, $p<0.001$) and 60 months follow-up (*A/B/C/D:* 19/6/0/0 vs 2/5/13/5, $p<0.001$).

IKDC objective stat. significant zugunsten IG

Health-related Quality of Life was assessed by the **KOOS subscale QoL** (*PROM*). At the 60-month follow-up, no statistically significant differences were observed between the IG and CG (*median [IQR]:* 85 [20] vs. 80 [39], $p=0.289$).

KOOS QoL nicht stat. signifikant

Safety[24]

Patients' safety was evaluated through *clinical outcomes*: adverse events, serious adverse events and the re-operation rate. No complications resulting from the BMAC harvesting procedure were observed, while stiffness requiring manipulation under anaesthesia was reported in one patient in the IG compared to zero patients in the CG. In the CG, four out of 25 patients underwent re-operation, while no patient in the IG required re-operation.

1 UE in IG, 4 Re-Operationen in KG

[24] This section addresses the assessment elements provided in Table A-19.

5 Certainty of evidence

Verzerrungspotenzial mit Cochrane RoB V2 und ROBINS-I bewertet

The risk of bias for individual outcomes of the included randomised and non-randomised studies was assessed with the Cochrane Risk of Bias 2 Tool [69] and the ROBINS-I [70] tool, respectively. Results of the critical appraisal of the included studies are presented in Table A-6 and Table A-7 in the Appendix.

Vertrauenswürdigkeit der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [71] for each endpoint individually. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [71].

GRADE uses four categories to rank the strength of evidence:

- **High**=We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate**=We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low**=Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low**=Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-8 to Table A-12

AMIC vs. MFx niedrige bis moderate Vertrauenswürdigkeit

Overall, the certainty of evidence of AMIC in comparison to microfracture is low to moderate and very low when AMIC is compared to autologous chondrocyte implantation.

AMIC+ vs. Standardtherapie: sehr niedrige Vertrauenswürdigkeit

The certainty of evidence for the effectiveness and safety of AMIC+ compared to AMIC, microfracture, or matrix-induced autologous chondrocyte implantation is very low.

Table 5-1: Summary of findings table AMIC vs. MFx

Outcome	Anticipated effects (AMIC vs. MFx)	Number of participants (studies)	Certainty	Comments
Physical function/ activity level/symptoms FU at ≤24 months	Two studies were able to detect a statistically significant difference in favour of the IG at 24m FU using the KOOS total (1 study) and IKDC score (1 study) **KOOS total** (2 studies, n=351): stat. significant in 1 study (MD 22.5; 95%CI: 17.0;28.0; **p<0.0001),** not stat. significant difference in another study (MD 1.9; 95%CI -3.9;7.7) **IKDC** (4 studies, n=505): Pooled MD across studies = 7.06 [95%CI: -3.9;18.0], high heterogeneity (I^2=92%); one study (included in pooled data) with significant MD between groups (MD: 22.7 (95%CI: 16.8-28.6; **p<0.001)** **WOMAC** (1 study, n=80): not stat. significant (MD=4.7; 95%CI: -7.22;16.62) **mCKRS** (1 study, n=47): not stat. significant (85 (±18) | NR vs. 74 (±26) **TAS** (1 study, n=124): not stat. significant (mean (range)): 4.0 (1.0-9.0) vs. 4.0 (2.0-8.0) **SF-36** (1 study, n=80): not stat. significant (MD=-1.8; 95%CI -5.9;2.3)	632 (6)	⨁⨁◯◯ Low	Lysholm score NR
Physical function/ activity level/symptoms FU at >24 months	One study was able to detect a stat. significant difference in favour of the IG at 120m FU using the Modified Cincinnati Scale. **mCKRS** (1 study, n=47): stat. significant at 120m FU (MD=26.9 [95%CI: 14.8;38.9], **p<0.05)** **WOMAC** (1 study, n=80): not stat. significant at 60m FU (MD=5.6; 95%CI: -5.7;16.8) **SF-36** (1 study, n=80): not stat. significant at 60m FU (MD=-1.4; 95%CI -5.7;2.8)	127 (2)	⨁⨁◯◯ very low	KOOS, TAS, IKDC NR
Pain FU at ≤24 months	None of the included studies reported stat. significant differences between groups at 24m FU using the VAS, KOOS pain and WOMAC pain. **VAS** (3 studies, n=585): pooled MD across studies = -2.27 [95%CI: -7.42; 2.9], low heterogeneity (I^2=17.8) **KOOS pain** (4 studies, n=505): not stat. significant (Altschuler mean: 89.5 vs 69.1); Glasbrenner median (IQR): 90.3 (82.5-95.2) vs. 91.8 (83.3-99.9); Kim (mean: 4.4 [95%CI: -1.2;9.9]); Kon (mean: 77.6 vs. 79.4) **WOMAC pain** (1 study, n=80): not stat. significant at 12m FU: MD=0.7 [95%CI: -2.6;4.0]	585 (5)	⨁⨁◯◯ Low	none
Pain FU at >24 months	None of the included studies reported stat. significant differences between groups at 24 to 120m FU using VAS and WOMAC pain **VAS** (1 study, n=47): not stat. significant (At 60 months: 11 (±20) | 15 (±22) vs. 30 (±19); 120 months: 12 (±21) | 11 (±16) vs. 31 (±20) **WOMAC pain** (1 study, n=80): not stat. significant (change after 60 months: MD=1.2 [95%CI: -2.5; 4.9])	127 (2)	⨁◯◯◯ very low	KOOS pain NR
HRQoL at ≤24 months	None of the included studies reported stat. significant differences between groups at 24m FU. **SF-36** (1 study, n=80): not stat. significant at 12m FU (MD=2.7; 95%CI: -1.9;7.3) **KOOS QoL** (3 studies, n=401): not stat. significant at 24m FU (mean: 73.9 vs 48.8); (median (IQR): 62.4 (48.6-71.9) vs. 68.8 (49.9-81.1); (mean: 54.1 vs 55.3)	481 (4)	⨁⨁◯◯ low	none
HRQoL at >24 months	None of the included studies reported stat. significant differences between groups at 24 to 120m FU **SF-36** (1 study, n=80): not stat. significant (Change after 60 months: MD=2.9 [95%CI: -1.5;7.2]	80 (1)	⨁◯◯◯ very low	KOOS QoL NR

Outcome	Anticipated effects (AMIC vs. MFx)	Number of participants (studies)	Certainty	Comments
Structural Repair at ≤24 months	Three studies were able to detect a stat. significant difference between groups at ≤24 months in defect filling **Defect filling** (Altschuler, Kim, Shive): stat. significant (at 24m FU: ≥75% defect fill: 88.5% vs. 30.9%, **p<.0001; at 24m FU:** <50%: 5 (6.1) vs. 14 (17.1), **p=0.0377**), at 12m FU 92.8 (±2.0) vs. 85.2 (±2.1), **p=0.011)** Three studies (n=201) did not detect a stat. significant difference between groups in defect filling**:** Volz: >66.7% defect filling: 60.0% vs. 25.0%; Glasbrenner: >50% of defect filling in both groups, Kon: mean %: 49.0 vs. 65.9) None of the studies reported stat. significant differences between groups in total MOCART scores at 24m FU. **MOCART** (1 study, n=100): not stat. significant (MD=5.2 [95%CI: -2.6;12.9])	632 (6)	⨁⨁⨁◯ moderate	Moderate certainty for defect filling, low certainty for total MOCART scores
Structural Repair at >24 months	One study was able to detect a stat. significant difference between groups at >24m FU in defect filling, favouring the IG. **Defect filling** (1 study, n=80): stat. significant (mean ±SD): At 60 months: 93.79 (±1.16) vs. 86.96 (±2.85), p=0.017 **MOCART** (1 study, n=47): not stat. significant (MD=-5 95%CI: -25.7;15.7)	127 (2)	⨁◯◯◯ very low	none
Necessity of joint replacement	None of the included studies reported stat. significant differences between groups at >24m FU. 1 study (n=47): not stat. significant (1 (5.9*) | 0 (0.0) vs. 0 (0.0)	47 (1)	⨁◯◯◯ very low	none
(Serious) adverse events	None of the included studies reported statistically significant differences between groups at 12 to 24m FU in (serious) adverse events. **Adverse events** (5 studies, n=532): not stat. significant (Altschuler: ≥1 AE in 98 (58.7) vs. 65 (77.4) patients; Volz: 13 adverse events in 9 pts.; Glasbrenner: 3 (25.0) vs. 3 (25.0); Kon: 13 (21.0) vs. 4 (6.5); Stanish: 12 months (41 vs. 37 pts.): 40 (98.0) vs. 36 (92.0)) **Serious adverse events** (6 studies, n=632): stat. not significant (Altschuler: ≥1 serious AE: 26 (15.6) vs. 17 (20.2); Volz: 0 (0.0) vs. 0 (0.0); Glasbrenner: 1 (8.3) vs 1 (8.3); Kim: 2 (4.4) vs. 2 (4.6); Kon: 3 (4.8) vs. 1 (1.6*); 12 months Stanish: 5 (12.2)30 vs. 1 (2.7)	632 (6)	⨁⨁◯◯ low	none

Abbreviations: AE … adverse event; AMIC … autologous matrix-induced chondrogenesis; CI … confidence interval; FU … follow-up; HRQoL … health-related quality of life; IG … intervention group; IKDC … International Knee Documentation Committee; IQR … interquartile range; KOOS … Knee Injury and Osteoarthritis Outcome Score; m … months; mCKRS – modified Cincinnati Knee Rating System; MD … mean difference; MFx … microfracture; MOCART … magnetic resonance observation of cartilage repair tissue; NR … not reported; pts … patients; QoL … quality of life; RCT … randomised controlled trial; SD … standard deviation; SF-36 … Short Form Health Survey; stat. … statistical/statistically; TAS … Tegner Activity Scale; VAS … Visual Analogue Scale; vs. … versus; WOMAC … Western Ontario McMaster Universities Osteoarthritis Index

Table 5-2: Summary of findings table AMIC vs. ACI

Outcome	Anticipated effects (AMIC vs. ACI)	Number of participants (studies)	Certainty	Comments
Physical function/ activity level/symptoms FU at ≤24 months	No statistically significant differences were found at 24m FU using the KOOS total and Lysholm score. **KOOS total:** mean delta between groups: 18.1 vs. 10.3, p=0.17 **Lysholm score:** mean (95% CI): 70.1 (61.0-79.6) vs. 69.6 (62.2 76.9); mean delta between groups: 19.7 vs. 17.0, p=0.66)	41 (1)	⨁◯◯◯ very low	KOOS, IKDC, TAS, mCKRS NR
Physical function/ activity level/symptoms FU at >24 months	NR	NR	NA	Longterm FU NR
Pain FU at ≤24 months	No statistically significant differences were found at 24m FU using the VAS and KOOS pain. **VAS.** mean (95%CI)): 27.0 (17.1-37.0) vs. 30.4 (20.1-41.2); MD at 24 months: 30.6 vs. 19.6, p=0.19 **KOOS pain:** Values NR (Subscales: at 24 months, the mean difference was higher in the AMIC group, but the difference was not statistically significant)	41 (1)	⨁◯◯◯ very low	WOMAC pain NR
Pain FU at >24 months	NR	NR	NA	Longterm FU NR
HRQoL at ≤24 months	NR	NR	NA	NR
Structural Repair	NR	NR	NA	NR
Necessity of joint replacement	NR	NR	NA	NR
(Serious) adverse events	No statistically significant differences were found at 24m FU. Serious adverse events: 0 (0.0) vs. 0 (0.0)	80 (1)	⨁◯◯◯ very low	AE NR

Abbreviations: ACI … autologous chondrocyte implantation; AE … adverse event; AMIC … autologous matrix-induced chondrogenesis; CI … confidence interval; FU … follow-up; HRQoL … health-related quality of life; IKDC … International Knee Documentation Committee; KOOS … Knee Injury and Osteoarthritis Outcome Score; m … months; mCKRS – modified Cincinnati Knee Rating System; MD … mean difference; NA … not applicable; NR … not reported; TAS … Tegner Activity Scale; VAS … Visual Analogue Scale; vs. … versus

Table 5-3: Summary of findings table AMIC+ vs. AMIC

Outcome	Anticipated effects (AMIC+ vs. AMIC)	Number of participants (studies)	Certainty	Comments
Physical function/ activity level/symptoms FU at ≤24 months	No statistically significant difference was found when comparing the Lysholm score between treatment groups at 24m FU. Group difference not statistically analysed for **IKDC objective** at 24m FU.	24 (1)	⨁◯◯◯ very low	KOOS and TAS NR
Physical function/ activity level/symptoms FU at >24 months	No statistically significant difference was found when comparing **Lysholm score** and **TAS** between treatment groups at 60 and 100m FU. Group difference not statistically analysed for **KOOS** (Symptoms, ADLs, Sport/rec.) at 60 and 100m FU.	24 (1)	⨁◯◯◯ very low	IKDC objective NR
Pain FU at ≤24 months	No statistically significant difference was found when comparing the **VAS** between treatment groups at 24m FU.	24 (1)	⨁◯◯◯ very low	KOOS pain NR
Pain FU at >24 months	No statistically significant difference was found when comparing the **VAS** and **KOOS pain** between treatment groups at 60 and 100m FU.	24 (1)	⨁◯◯◯ very low	none
HRQoL >24	Group difference not statistically analysed for **KOOS QoL** at 60 and 100m FU.	24 (1)	⨁◯◯◯ very low	SF-Health Survey + ≤24m NR
Structural Repair	Group difference not statistically analysed, even if MRI showed similar defect size and filling in both groups at 24m FU.	24 (1)	⨁◯◯◯ very low	MOCART + > 24m NR
Necessity of joint replacement	NR	24 (1)	NA	NA
(Serious) adverse events	Group difference not statistically analysed at any time point. AE at 12m FU (0 vs. 1)	24 (1)	⨁◯◯◯ very low	Serious AE NR

Abbreviations: ADL … activities of daily living; AE … adverse event; AMIC … autologous matrix-induced chondrogenesis; AMIC+ … autologous matrix-induced chondrogenesis with bone marrow aspirate concentrate; FU … follow-up; HRQoL … health-related quality of life; IKDC … International Knee Documentation Committee; KOOS … Knee Injury and Osteoarthritis Outcome Score; m … months; MRI … magnetic resonance imaging; MOCART … magnetic resonance observation of cartilage repair tissue; NR … not reported; PRO … patient reported outcome; QoL … quality of life; rec. … recreation; SAF … safety; SF … Short Form; TAS … Tegner Activity Scale; VAS … Visual Analogue Scale; vs. … versus

Table 5-4: Summary of findings table AMIC+ vs. MACI

Outcome	Anticipated effects (AMIC+ vs. MACI)	Number of participants (studies)	Certainty	Comments
Physical function/ activity level/symptoms FU at ≤24 months	Group difference not statistically analysed for **KOOS** (Symptoms, ADLs, Sport/rec.), **IKDC** objective/subjective and **TAS** at 24m FU.	37 (1)	⨁◯◯◯ very low	Lysholm NR
Physical function/ activity level/symptoms FU at >24 months	No statistically significant difference was found when comparing the **KOOS** (Symptoms, ADLs, Sport/rec), IKDC objective and TAS between treatment groups at final FU. **IKDC Subjective:** stat. significant at final FU (82.52 ±10.72 vs. 75.70 ±9.85, **p=0.015**)	37 (1)	⨁◯◯◯ very low	Lysholm NR
Pain FU at ≤24 months	Group difference not statistically analysed for KOOS pain and VAS at 24m FU.	37 (1)	⨁◯◯◯ very low	none
Pain FU at >24 months	**VAS:** not stat. significant at final FU (0.3 ±0.7 vs. 0.8 ±0.7, p=0.418) Group difference not statistically analysed for **KOOS pain** at final FU.	37 (1)	⨁◯◯◯ very low	none
HRQoL ≤24	The group difference not statistically analysed in KOOS QoL at 24 m FU.	37 (1)	⨁◯◯◯ very low	SF-Health Survey NR
HRQoL >24	**KOOS QoL:** not stat. significant at final FU (84.0 ±14.8 vs. 76.1 ±16.9, p=0.107)	37 (1)	⨁◯◯◯ very low	SF-Health Survey NR
Structural Repair	Group difference not statistically analysed for MRI at final FU.	37 (1)	⨁◯◯◯ very low	> 24m + MOCART NR
Necessity of joint replacement	NR	NR	NA	NR
(Serious) adverse events	No adverse reactions or postoperative infections were noted	37 (1)	⨁◯◯◯ very low	Serious AE NR

Abbreviations: ADL … activities of daily living; AE … adverse event; AMIC+ … autologous matrix-induced chondrogenesis with bone marrow aspirate concentrate; FU … follow-up; HRQoL … health-related quality of life; IKDC … International Knee Documentation Committee; KOOS … Knee Injury and Osteoarthritis Outcome Score; m … months; MACI … matrix-induced autologous chondrocyte implantation; MRI … magnetic resonance imaging; MOCART … magnetic resonance observation of cartilage repair tissue; NR … not reported; QoL … quality of life; rec. … recreation; SF … Short Form; stat. … statistical/statistically; TAS … Tegner Activity Scale; VAS … Visual Analogue Scale; vs. … versus

Table 5-5: Summary of findings table AMIC+ vs. MFx

Outcome	Anticipated effects (AMIC+ vs. MFx)	Number of participants (studies)	Certainty	Comments
Physical function/ activity level/symptoms FU at ≤24 months	**IKDC objective:** stat. significant when comparing treatment groups at 24m FU (16/9/0/0 vs. 4/12/9/0, **p<0.001**). No statistically significant difference was found when comparing the TAS and Lysholm between treatment groups at 24m FU.	52 (1)	⨁◯◯◯ very low	KOOS subscales NR
Physical function/ activity level/symptoms FU at >24 months	**IKDC objective:** stat. significant when comparing treatment groups at 60m FU (19/6/0/0 vs. 2/5/13/5, **p<0.001**). **KOOS Sport/rec:** stat. significant when comparing treatment groups at 60m FU (*median [IQR]:* 85 [17] vs. 68 [37], **p=0.013**) **TAS:** stat. significant when comparing treatment groups at 60m FU (*median [IQR]:* 6 [1.5] vs 4 [2], **p<0.001**). No statistically significant difference was found when comparing KOOS (Symptoms, ADLs), IKDC subjective and Lysholm between treatment groups at 60m FU.	52 (1)	⨁◯◯◯ very low	none
Pain FU at ≤24 months	NR	NR	NA	NA
Pain FU at >24 months	**KOOS pain:** stat. significant when comparing treatment groups at 60m FU (*median [IQR]:* 95 [10] vs. 87 [31], **p=0.023**).	52 (1)	⨁◯◯◯ very low	VAS NR
HrQoL	**KOOS QoL**: stat. not significant at 60m FU (*median [IQR]:* 85 [20] vs. 80 [39], p=0.289).	52 (1)	⨁◯◯◯ very low	≤24m + SF-Health Survey NR
Structural Repair	NR	NR	NA	NA
Necessity of joint replacement	NR	52 (1)	⨁◯◯◯ very low	
(Serious) adverse events	AE (1 vs. 0), no serious AE	52 (1)	⨁◯◯◯ very low	

Abbreviations: ADL … activities of daily living; AE … adverse event; AMIC+ … autologous matrix-induced chondrogenesis with bone marrow aspirate concentrate; FU … follow-up; HRQoL … health-related quality of life; IKDC … International Knee Documentation Committee; IQR … interquartile range; KOOS … Knee Injury and Osteoarthritis Outcome Score; m … months; MFx … microfracture; NA … not applicable; NR … not reported; PRO … patient reported outcome; QoL … quality of life; rec. … recreation; SAF … safety; SF … Short Form; stat. … statistical/statistically; TAS … Tegner Activity Scale; vs. … versus

6 Discussion

8 RCTs und 2 NRCTs eingeschlossen

The objective of this HTA was to evaluate the comparative effectiveness and safety of one-stage matrix-assisted cartilage repair (autologous matrix-induced chondrogenesis, AMIC) and AMIC+ which combines the procedure with bone marrow aspirate concentrate (BMAC) in the knee. These procedures are compared to standard surgical procedures encompassing microfracture (MFx) or two-stage matrix-assisted cartilage repair. A total of eight randomised controlled trials and two observational studies with concurrent controls met our pre-defined eligibility criteria. For the standard AMIC procedure, this review is considered an update on a previous report from 2019 [37]. Therefore, this review included three previously assessed RCTs and their follow-ups.

Summary of Findings AMIC

7 RCTs zu AMIC verglichen mit Standardtherapie

Overall, this systematic review included seven RCTs investigating AMIC for cartilage repair, with six studies (n=632) comparing AMIC versus MFx and one study (n=41) comparing AMIC versus autologous chondrocyte implantation (ACI). The included participants had cartilage defects in the knee ICRS grade III and IV with lesion sizes ranging from 2.3 to 4 cm^2 in the intervention group (IG) and 1.9 to 4.7 cm^2 in the control group (CG). One study [91] reported a maximum lesion size of 9 cm^2 versus 12.8 cm^2. Most studies reported outcomes up to 24 months, with some providing long-term follow-up data at 60 and 120 months.

AMIC versus MFx

AMIC vs. MFx: keine stat. signifikanten Unterschiede bei Schmerzskalen, jedoch mögliche klinische Relevanz

stat. signifikante Unterschiede bei struktureller Wiederherstellung

There was low certainty of evidence (5 studies, n=585), and no statistically significant differences between groups in pain measures (KOOS pain, VAS, WOMAC pain) at the 24-month follow-up, however when changes are considered against established minimal clinically important differences (MCIDs), individual improvements within groups may have reached clinical relevance. The overall certainty of evidence for the long-term follow-up (24 to 120 months) was very low. Structural repair assessment demonstrated statistically significant improvements in defect filling favouring AMIC in three out of six studies with low to moderate certainty of evidence after 24 months. According to expert input, this outcome is expected to show even better results in the long-term, as improved structural repair is associated with better biomechanical tissue properties, potentially leading to more sustainable clinical outcomes compared to treatments like MFx, where results tend to deteriorate after 2 years.

1 von 6 Studien berichtet stat. signifikante Unterschiede und erreichte klinische Relevanz beim KOOS zugunsten AMIC

Regarding function, low certainty of evidence (6 studies, n=632) indicates no statistically significant differences in various outcome measures (IKDC, WOMAC, TAS, ICRS). Also, pooled data for IKDC did not show statistically significant differences at 24 months follow up. Yet, one study (n=251) found significant improvements favouring AMIC in total KOOS scores at 24 months [45]. The Modified Cincinnati Knee Rating System showed significant long-term benefits for AMIC at 120 months; however, it was based on very low certainty of evidence (1 study, n=47). Considering the established MCIDs for IKDC and KOOS, the MCID was not reached for IKDC, suggesting no clinical relevance, but this threshold was exceeded for the KOOS.

Health-related quality of life (HRQoL, quality of life – QoL), measured by KOOS QoL and SF-36, showed mixed results with one study [45] including 251 patients reporting superiority of AMIC (KOOS QoL: 73.9 vs. 48.8) with also exceeding the MCID, also suggesting clinical relevance, while others found neither significant differences between groups nor clinical relevance.

stat. signifikante und klinisch relevante Ergebnisse beim KOOS QoL zugunsten AMIC

Safety assessments showed adverse events (5 studies, n=532) ranging from 0% to 60% in the IG and 0% to 77% in the MFx group at 24 months. One study [92, 93] reported adverse events of up to 98% versus 92% of patients, also comprising arthralgia and nausea. Serious adverse events occurred in 0-15.6% of AMIC patients versus 0-20.2% in MFx patients. Reoperation rates varied, with one study [45] showing significantly fewer treatment failures in the IG (7.2% vs. 21.4%, $p=0.002$). The overall certainty of evidence was very low.

UE: 0-60 % vs. 0-77 %

SUE: 0-15,6 % vs. 0-20,2 %

AMIC versus ACI

Based on overall very low certainty of evidence (1 study, n=41), similar outcomes were yielded across study groups in the included study [49]. Pain scores and functional outcomes (KOOS total, Lysholm Score) at 24 months were comparable between groups. HRQoL was not assessed. Safety outcomes were similar, with no serious adverse events reported. There were comparable re-operation rates (re-arthroscopy: 14.3% vs. 15.0%; reoperations: 4.8% vs. 5.0%).

AMIC vs. ACI: sehr niedrige Vertrauenswürdigkeit, keine stat. signifikanten Unterschiede bei allen Endpunkten

Summary of Findings AMIC+

The effectiveness and safety of AMIC with the augmentation of bone marrow aspirate concentrate (AMIC+) was assessed by one randomised controlled trial (RCT) and two non-randomised controlled trials (NRCTs). One study compared AMIC+ to the standard AMIC (RCT), including 24 patients in total. The NRCTs used MFx and matrix-assisted chondrocyte implantation (MACI) as comparators and were based on total sample sizes of 37 and 52 patients, respectively. The included participants had cartilage defects in the knee with ICRS grade III and IV, with differences in defect size, ranging from mean 3.6 cm^2 (RCT) to 6.3 cm^2 (NRCT) or median 5.5 cm^2 (NRCT) as mean of intervention and CG. The follow-up duration ranged from 54.7 months on average to 100 months.

AMIC+ vs AMIC (1 RCT), MACI (1 NRCT), MFx (1 NRCT)

AMIC+ versus AMIC

The findings, based on a single randomised controlled trial (n=24) with very low certainty of evidence across all measured endpoints, indicate an absence of significant differences between AMIC+ and AMIC at all time points. This includes outcomes such as morbidity, as assessed by KOOS pain (60 and 100 months follow-up), VAS (at 24, 60 and 100 months follow-up), and structural repair (MRI), as well as function, as evaluated by KOOS Symptoms, ADLs and Sport/rec (at 60 and 100 months follow-up), TAS (60 and 100 months follow-up), Lysholm score (at 24, 60 and 100 months follow-up), and IKDC objective (at 24 months follow-up). Furthermore, the study did not reveal differences between groups in terms of quality of life (KOOS QoL at 60- and 100-months follow-up), and the safety of the patients in both groups was comparable, assessed by the occurrence of adverse events. It should be noted that group differences were not statistically analysed for some outcomes, including IKDC objective, KOOS subscales, MRI and adverse events.

sehr niedrige Evidenzsicherheit bei allen Endpunkten (RCT)

Wirksamkeit: kein Endpunkt zeigt signifikanten Unterschied zw. AMIC+ und AMIC

Sicherheit: in beiden Gruppen vergleichbar

AMIC+ versus MACI

Based on low certainty of evidence regarding all endpoints, there is an absence of significant evidence to suggest a difference between AMIC+ and MACI (1 NRCT, n=37), with a single exception for IKDC subjective, indicating better knee function for AMIC+ than MACI (mean ±SD: 82.52 ±10.72 vs. 75.70 ±9.85, $p=0.015$) at the final follow-up (min. 36 months; mean: 54.16 vs. 59.69 months). For the other scores measuring function, including KOOS subscales, IKDC and TAS, the differences between the two groups were either not statistically analysed (at 24 months follow-up) or statistically insignificant (final follow-up). No group differences were analysed for pain and QoL after 24 months either. Morbidity-related long-term outcomes (final follow-up) of VAS pain scales did not achieve a statistically significant difference between the groups, despite the potential of AMIC+ to yield superior outcomes in terms of structural repair when compared to MACI, exhibiting 81% defect filling (compared to 76%) and complete integration with adjacent cartilage in 93.7% (compared to 88.2%). Additionally, no evidence was found to suggest that AMIC+ outperformed MACI in terms of HRQoL, as assessed by KOOS QoL at the final follow-up. The safety of patients in both groups was comparable because no adverse reactions or postoperative infections were noted.

sehr niedrige Evidenzsicherheit bei allen Endpunkten (NRCT)

Wirksamkeit: kein Endpunkt zeigt signifikanten Unterschied zw. AMIC+ und MACI mit Ausnahme IKDC subjective (Funktion)

AMIC+ versus MFx

The results of the comparison between AMIC+ and MFx (1 NRCT, n=52) are based on very low certainty of evidence for all endpoints. Within the morbidity endpoint, the AMIC+ group demonstrated a lower level of pain (KOOS pain) compared to the AMIC group at 60 months follow-up (*median [IQR]:* 95 [10] vs. 87 [31], $p=0.023$). Across three outcome measures of function, a statistically significant difference between the two groups was found in favour of AMIC+. At 24 and 60 months follow-up, the IKDC objective revealed a significantly higher proportion of patients categorised as normal or nearly normal (out of additional abnormal and severely abnormal) compared to the MFx ($p<0.001$). In addition, the KOOS Sport/rec and TAS showed higher scores for AMIC+ at 60 months follow-up (*median [IQR]:* 85 [17] vs. 68 [37], $p=0.013$; and 6 [1.5] vs. 4 [2], $p<0.001$), indicating superior function in comparison to MFx. However, no evidence was found for the superiority of one group over the other in terms of HRQoL. With regard to patient safety, no group difference was analysed, although one adverse event occurred in the AMIC+ group, and four patients required re-operation, compared to zero events in the other group.

sehr niedrige Evidenzsicherheit bei allen Endpunkten (NRCT)

Wirksamkeit: signifikanter Unterschied zw. AMIC+ und MFx bei IKDC objective (24, 60 m), KOOS sports/rec + TAS (60 m); Wirksamkeit: kein signifikanter Unterschied: KOOS pain + QoL; Sicherheit: Gruppenunterschied nicht analysiert

Internal validity, external validity and evidence gaps

The internal validity of randomised controlled trials was assessed with the Cochrane Risk of Bias tool v.2 for RCTs and ROBINS-I for NRCTs. Across trials, there was a similar trend towards increased risk of bias in patient-reported outcomes and clinical endpoints. Among RCTs, three studies demonstrated some concerns, while six studies revealed a high risk of bias for patient-reported outcomes. Assessment of clinical outcomes was similar, with four RCTs showing some concerns and five displaying a high risk of bias. For one RCT, the risk of bias increased from "some concerns" in the primary study to "high" in the follow-up assessment. In the case of non-randomised controlled trials, the quality was mixed: one study demonstrated a moderate risk of bias for both patient-reported and clinical outcomes, while the other showed a critical risk of bias concerns.

moderates (3 RCTs, 1 NRCT) bis hohes (6 RCTs, 1 NRCT) Verzerrungsrisiko bei patient:innenberichteten Endpunkten

Gründe dafür v. a. fehlende Verblindung

Main reasons for increased risk of bias were lack of blinding (being particularly problematic in patient-reported outcomes) [43-45, 88, 89, 91-93] and high drop-out rates in some trials [43, 91]. The risk of bias assessment largely led to a very low to low certainty of evidence (GRADE), which was further reduced, particularly in AMIC+, by the failure to reach the optimal information size we calculated.

Problem der Multiplizität

strukturelle Wiederherstellung als Surrogatendpunkt, zeigt dennoch große Unterschiede zugunsten AMIC

The use of multiple (validated) outcome measures for one outcome in primary studies was a further limitation of the evidence, potentially increasing the risk of multiplicity [97]. While outcomes like KOOS pain and VAS were commonly reported, some critical outcomes were only sparsely documented-for instance, the necessity of total joint replacement was reported in just one study out of seven. The reporting of structural repair, while covered in six studies, used varying assessment methods, with only two studies providing complete MOCART scores. Although structural repair is considered a surrogate outcome, the results consistently demonstrated superiority of AMIC over MFx in this domain. Importantly, these structural assessments were mostly conducted by blinded clinicians, enhancing their reliability. In contrast, patient-reported outcomes may have been influenced by treatment awareness, as most patients knew which intervention they received. Beyond structural improvements, the safety profile also suggests potential advantages for AMIC compared to standard treatments.

Evidenzlücken:

In light of AMIC trials, we found further evidence gaps that address the external validity:

- Unsicherheit bezüglich Langzeiteffekten

  Increased uncertainty for long-term effectiveness: Most of the studies selected a primary follow-up of up to 24 months. Although some long-term follow-up data are available, these results are prone to bias mainly due to a high loss to follow-up rate and the nature of post-hoc analyses.

- Evidenz primär zu AMIC vs. MFx

  The evidence is applicable mainly to the comparison AMIC versus MFx (6 out of 7 [43-45, 88-93]). Evidence is sparse for other comparisons, such as two-stage cartilage matrix repair techniques.

- unterschiedliche Defektgrößen und Lokalisationen innerhalb der Studien

  The evidence showed considerable variation in both the size and location of cartilage defects. As a result, it is not possible to determine which specific defect characteristics (size or location) would benefit most from AMIC treatment. Interestingly, while MFx is traditionally indicated for smaller lesions (<2 cm^2), the mean lesion sizes in most studies exceeded this size (5 out of 7, [43-45, 91, 96]). According to expert input, this heterogeneity is a recognised problem in cartilage repair studies, as defect sizes are often underestimated in preoperative MRI and are only accurately assessed during surgery. Additionally, the larger the cartilage defect, the less effective MFx tends to be, which creates both ethical challenges in study design and potential advantages for demonstrating treatment differences.

- unterschiedliche Materialien für Matrizen

  The evidence demonstrated variation in scaffold materials, preventing clear conclusions about which material characteristics might yield optimal outcomes.

The following evidence gaps addressing the external validity were identified for AMIC+ studies:

- limitierte Studien zu AMIC+ mit sehr niedriger Vertrauenswürdigkeit der Evidenz

  The findings for AMIC+ are derived from a limited number of studies (n=3) with low patient numbers, and the certainty of the evidence across all endpoints is very low. Based on a single non-randomised trial, only enhanced function at 24 and 60 months following AMIC+

surgery in comparison to MFx could be substantiated. Consequently, further evidence is requisite to ascertain the efficacy of AMIC+.

- The decision to include the underlying AMIC standard therapy in the benefit catalogue may have implications for the focus of future research. If the intervention is to be refunded, then a comparison of AMIC+ versus AMIC should be a priority. If it is not, then the existing standard of care, such as MFx or MACI, should be used as a comparison group.

Standardtherapie abhängig von Refundierungs-entscheidungen

- Evidence is sparse for all comparisons due to a single study for each, namely AMIC, MACI and MFx.

wenig Evidenz vorhanden

Embedding our study into existing knowledge

früherer LBI-HTA Bericht inkludierte auch zweizeitige Verfahren

In 2019, the previous LBI-HTA report on cartilage repair [37] was published, focusing not only on one-stage procedures in the knee but also on two-step procedures across knee and ankle joints. Regarding effectiveness, a superiority of AMIC compared to MFx could not be determined. This contrast to our findings might be attributed to the inclusion of additional recent evidence in our review. Furthermore, while the previous report highlighted a complete lack of evidence comparing AMIC to ACI, our review included one small trial making this comparison, though the evidence remains limited.

mittlerweile mehr Evidenz zu AMIC vs. MFx

Bericht des National Institute for Health and Care Excellence (NICE) inkludierte auch systematische Übersichtsarbeiten

In 2024, the National Institute for Health and Care Excellence (NICE) conducted an interventional procedure overview of single-step scaffold insertion for repairing symptomatic chondral knee defects [41]. NICE also summarised evidence covering not only matrices but also injectable gel. However, NICE included a total of five systematic reviews and four RCTs, with the systematic reviews also comprising non-comparative studies. The NICE report reviewed evidence from about 7,000 patients. Studies with two to seven years follow-up showed significant improvements in pain, function and activity levels, with the scaffold procedure often performing better than microfracture alone. Surgical failure rates were low (2-7%), with transient knee pain being the most common complication and serious complications rare. While the evidence suggests this is a beneficial procedure with acceptable safety, research is still needed on long-term outcomes and optimal patient selection. Different scaffold materials and surgical techniques were used across studies.

möglicher Zusatznutzen von AMIC

fehlende Langzeitdaten

NICE: AMIC als Brücke zwischen MFx und komplexen Therapien

In the NICE report [41], it is further acknowledged that according to clinical experts, the procedure serves as an intermediate treatment option, bridging the gap between microfracture (used for smaller defects) and more complex treatments such as cell-based therapies or resurfacing procedures (typically reserved for larger lesions). Based on the evidence report, NICE states that using single-step scaffold insertion is an option for repairing symptomatic chondral knee defects provided standard arrangements for clinical governance, consent and audit are in place.

systematische Übersichtsarbeit zu mehreren OP-Techniken fanden keine stat. signifikanten Unterschiede zwischen den Gruppen

Another systematic review and network meta-analysis [98] comparing surgical techniques for knee chondral defects, including MFx, AMIC, osteochondral autograft transplantation (OCT), and ACI. The study analysed 19 randomised controlled trials with 1,149 knees (patient number not reported). The analysis [98] found no significant differences between treatments in patient-reported outcome measures at any time point. Interestingly, authors reported lower failure and reoperation rates in chondrospheres (used in ACI procedures compared to other treatments such as AMIC), though this finding should be interpreted cautiously due to heterogeneous adverse event report-

ing across studies. Authors reported that most trials were open-label and non-blinded, resulting in a high risk of bias. The researchers emphasised the need for standardisation in reporting both efficacy outcomes and safety measures in future clinical trials to enable more reliable treatment comparisons and better inform clinical decision-making.

Meta-Analyse zu AMIC+ berichtete vergleichbare Ergebnisse zwischen den Gruppen

Considering the AMIC+ evidence, in 2023, a meta-analysis [47] comparing scaffold-implanted mesenchymal stem cells with cell-free scaffolds and with and without BMAC augmentation for treating knee chondral defects was conducted. The study analysed 39 studies (predominantly single-arm trials) and included 965 patients. The authors found similar results, reporting comparable improvements in pain, activity scores, defect filling and necessity of total joint replacement across treatments. Authors reported that there was a high heterogeneity in lesion sizes and follow-up times between groups.

Ongoing randomised controlled trials

5 laufende RCTs (4 AMIC; 1 AMIC+)

Vollendung: 2025-2032

Several randomised controlled trials are currently evaluating single-step scaffold procedures for knee cartilage defects. Four trials are investigating AMIC techniques: a study comparing AMIC to matrix-assisted autologous chondrocyte transplantation in 80 patients with large cartilage defects (completion 2032), a 185-patient trial evaluating JointRep™ with microfracture (completion 2025), a comparison of engineered cartilage graft with AMIC in 150 patients with patellofemoral osteoarthritis (completion 2030), and a 100-patient trial assessing modified microfracture using CartiFill™ with microfracture (completion 2027). Additionally, one trial is investigating AMIC augmented with cell suspensions (AMIC+), comparing Hyalofast® with bone marrow aspirate concentrate to microfracture in 200 patients (completion 2026). Most trials use patient-reported outcomes related to function or pain (e.g., KOOS scores) as primary endpoint. The reader is referred to Table A-15 and Table A-16 for more information on currently ongoing studies.

Limitations

Limitationen: nur Studien in englischer oder deutscher Sprache inkludiert

Ausschluss von Studien, die nur Surrogatendpunkte berichteten

Heterogenität in der Berichterstattung

This systematic review should be viewed in light of its limitations. Although our systematic search was not language inclusive, the focus on English (and German) language publications likely captured the most relevant evidence, given the international nature of orthopaedic research. The inclusion of randomised controlled trials for AMIC and randomised and non-randomised controlled trials for AMIC+ aligns with established standards for comparative effectiveness research [97]. While studies focusing solely on surrogate endpoints were excluded (e.g. [99], this strengthened our assessment of comparative effectiveness. We evaluated bone marrow aspirate concentrate as an augmentation, though other biomaterials exist that were beyond our review scope [100] [101]. For transparency, one study previously classified as an RCT [102] was excluded after careful assessment by three independent reviewers determined it did not meet RCT criteria. Another limitation was a heterogeneity in outcome reporting, with some results presented only in graphical format, we extracted numerical data using WebPlotDigitizer [103] to enable comparisons. In addition, this heterogeneity could also be displayed in the meta-analysis.

Conclusions

mögliche Überlegenheit von AMIC gegenüber MFx in struktureller Wiederherstellung; vergleichbare oder bessere Ergebnisse in anderen Endpunkten für AMIC

unzureichende Langzeitdaten und Daten zu AMIC verglichen mit ACI

The available evidence indicates that autologous matrix-induced chondrogenesis (AMIC) may be more effective than microfracture (MFx) in terms of structural repair, which is, however a surrogate outcome that may not sufficiently translate into patient-relevant improvements. Considering other outcomes comparable or better results may be achieved with AMIC. Due to limited long-term data and high loss to follow-up in extended observations, the currently available trial results do not provide robust evidence of long-term effectiveness beyond 24 months. Uncertainty remains about which specific patient populations would benefit most from AMIC, particularly regarding defect size and location characteristics. While several studies assessed patient-reported outcomes, the evidence was insufficient to determine the necessity of total joint replacement, as this was reported in only one study. Evidence comparing AMIC to autologous chondrocyte implantation is inconclusive, as it is based on only one small study.

unzureichende Evidenz für AMIC+

For AMIC augmented with bone marrow aspirate concentrate (AMIC+), evidence is particularly limited, with only three small studies showing mixed results. Future trials should focus on standardised outcome reporting, longer follow-up periods, and better characterisation of patient and defect characteristics to determine optimal indications for treatment.

7 Evidence-based conclusion

In Table 7-1 and Table 7-2 the schemes for recommendations are displayed and the according choices are highlighted.

Table 7-1: Evidence based conclusion AMIC

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
X	2b	**Less robust evidence indicating an added benefit in routine use or in specific indications**
	3	No evidence or inconclusive evidence available to demonstrate an added benefit of the intervention of interest.
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

Evidenz deutet auf Zusatznutzen von AMIC gegenüber MFx hin

The current evidence indicates that AMIC may be more effective than MFx in terms of structural repair. For patient-reported function, the evidence showed mixed but generally comparable or slightly better results for AMIC compared to MFx. The evidence further indicates that AMIC may be safer than MFx in terms of a reduced risk for treatment failures, although it is unclear whether this is generalisable to some or all patients with an indication for cartilage repair.

unzureichende Evidenz für andere Vergleiche

For other comparisons, such as AMIC versus two-stage cartilage repair, the evidence is insufficient to indicate superiority, inferiority or equivalence.

Neubewertung für 2033 empfohlen

Re-evaluation is recommended in 2033.

Table 7-2: Evidence based conclusion AMIC+

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
	2b	Less robust evidence indicating an added benefit in routine use or in specific indications
X	3	**No evidence or inconclusive evidence available to demonstrate an added benefit of the intervention of interest.**
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

unzureichende Evidenz für AMIC+

The current evidence is not sufficient to prove that the assessed technology AMIC+ is more effective and safer than the comparators AMIC, MACI and MFx. Results are based on a very low certainty of evidence across all endpoints. New study results will potentially influence the effect estimate considerably.

The re-evaluation is recommended in 2028, if updated knowledge on the added benefit of AMIC+ is required, provided that the RCT is completed. If re-evaluation is considered in conjunction with AMIC, re-evaluation is suggested for 2033.

Neubewertung: 2028 bei Vorliegen neuer Ergebnisse

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Appendix

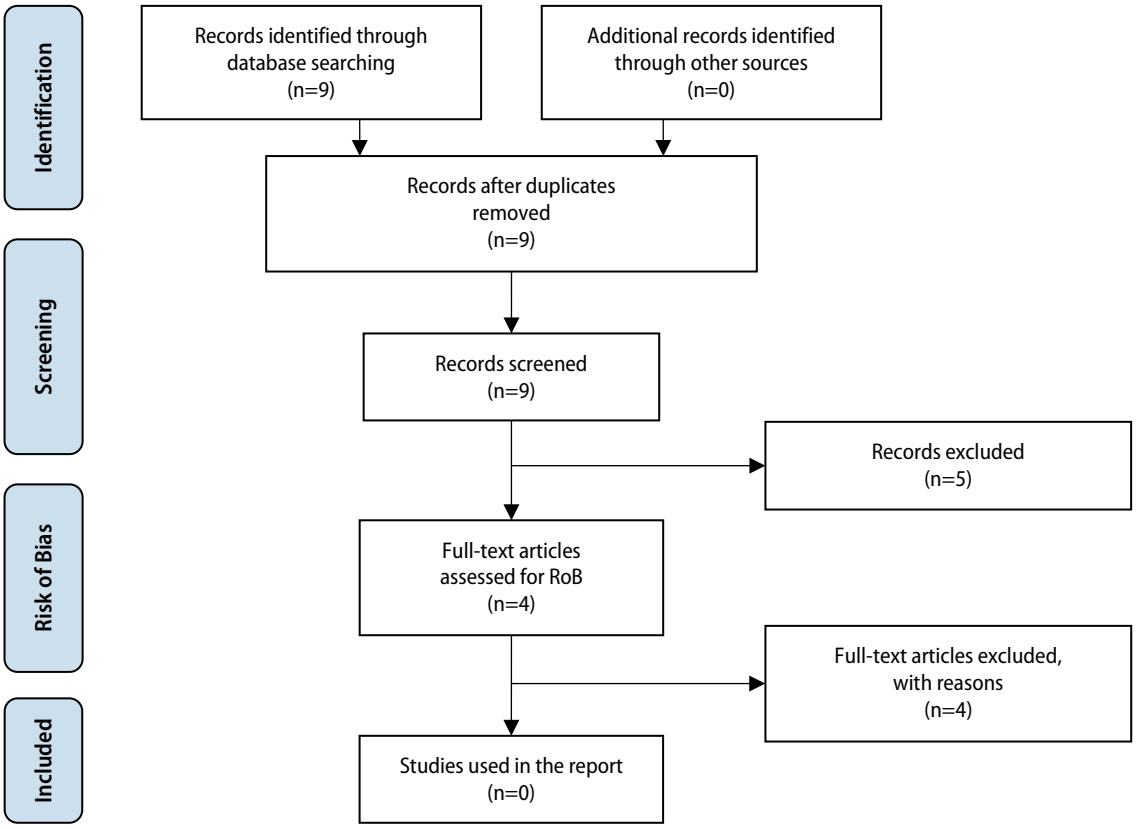

Figure A-1: Flow chart of study selection in preliminary search (PRISMA Flow diagram)

Preliminary Search

Table A-1: Concerns and rationales for the exclusion of Systematic Reviews [65]

SR	NICE, 2024 [41]	Ow, 2023 [47]	Palka, 2024 [100]	Valisena, 2024 [98]
Concerns				
Domain 1	unclear	high	low	low
Domain 2	high	high	high	low
Domain 3	high	high	low	low
Domain 4	high	high	high	high
RoB in the review	high	high	low	low
Overall rationales for exclusion				
	Despite the presence of indication in the method manuals, no assessment of risk of bias could be identified. Studies published prior to 2023 were excluded from the analysis.	No pre-registered protocol. Inadequate risk of bias tools.	Comparison of MFx vs AMIC. The PICO is therefore defined more narrowly than is necessary for this report, which is why the SR could not be used.	No consideration of BMAC; no direct comparison, as network analysis was carried out.

Abbreviations: AMIC … autologous matrix-induced chondrogenesis; BMAC … bone marrow aspirate concentrate; MFx … microfracture; NICE … National Institute for Health and Care Excellence; RoB … Risk of Bias; SR … systematic review

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-2: One-stage matrix assisted cartilage repair: Results from randomised controlled trials

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
NCT	**NCT03299959**	**NCT02993510**		**NCT01458782**
Country	Italy	Germany		Norway
Sponsor	The present trial was fully funded by Cartiheal Ltd, Israel.	Geistlich Pharma AG, Switzerland		NR
Intervention/Product	Aragonite-based scaffold (Agili-c-implant)/ NR Mini-open/open procedure, no microfracture	AMIC (Chondro-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland): Miniarthrotomy + microfracture + collagen type I/III membrane (AMIC® sutured | AMIC® glued)		AMIC (Chondro-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland): small arthrotomy, debridement, drilling, scaffold was sutured and glued
Comparator	Arthroscopic debridement/microfractures alone (debridement: removing the damaged and unstable cartilage fragments from the articular surface; microfracture: penetrating the subchondral bone with a dedicated pick	Arthroscopic MFx alone		2-step surgery: Second generation ACI: chondrocytes harvested 3 to 4 weeks prior to index surgery. Cells were infected under the sutured collagen patch
Study design	Multicentre randomised controlled trial	Two-centred, prospective, randomised controlled trial (RCT)		Single centre randomised controlled trial
Study duration[26]	2017-2019	2004-2010		2011-2014
Blinding	None (open-label)	Neither patients or physicians were blinded		None (open label)
Number of pts at randomisation Total (IG vs. CG)	251 (167 vs. 84)	47 (17 | 17[27] vs. 13)[28]		41 (20 vs. 21)
Female, n (%)	60 (35.9) vs. 33 (39.3)	2 (11.8*) | 5 (29.4*) vs. 3 (23.1*)		12 (60) vs. 7 (33.3)
Inclusion criteria	■ aged 21 -75 yrs ■ presence of up to 3 joint surface lesions ICRS grade 3a or above on the femoral condyles or trochlea, ■ total treatable area of 1 to 7 cm2, patients physically and mentally willing and able to comply with the postoperative rehabilitation protocol and scheduled clinical and radiographic visits ■ nonresponsive to physical therapy for at least 3 to 4 weeks.	■ aged 18-50 yrs, ■ one or two isolated cartilage defects of the knee grade III or IV according to the Outerbridge classification, ■ located either on the medial or lateral femoral condyle, trochlea or patella, ■ defect size between 2 and 10 cm^2		■ aged 18-60 yrs ■ informed consent signed by patient ■ symptomatic cartilage defects of the knee > $2cm^2$ ■ ≥1 chondral/osteochondral lesions of the distal femur and/or patella as identified by MRI findings and/or previous arthroscopies

[25] Baseline information and 5 year-follow-up data was extracted from Volz 2017. Information for the 10 year-follow up from Volz 2024.

[26] Enrolment period.

[27] In 17 patients the scaffold was sutured and in 17 patients the scaffold was glued.

[28] In this study there are two intervention groups. The data will be reported as follows: AMIC glued | AMIC sutured vs. MFx).

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
Inclusion criteria *(continuation)*				■ Pts with signs of early osteoarthritis (symptoms caused by ≥1 isolated cartilage defect suitable for biological repair
Exclusion criteria	■ KOOS Pain Subscale score at baseline is less than 20 or more than 65 (scale: maximum pain = 0, pain free = 100) ■ Bony defect depth deeper than 8mm, according to baseline MRI/X-ray/arthroscopy; Articular cartilage lesions in the tibia or the patella, ICRS grades IVa or above, severe OA of the index knee, graded 4 according to the KL score ■ significant instability of the index knee according to IKDC Knee Examination Form 2000, grade C (abnormal) or D (severely abnormal) ■ >8° varus or >8° valgus malalignment according to standing radiograph ■ lack of functional remaining meniscus, >5-mm rim at the end of the procedure ■ any known history of intra-articular or osseous infection of the index knee ■ uncontained lesion – lack of vital bone wall ≥2 mm thick completely surrounding the lesion – based on MRI, radiograph, or arthroscopy ■ inability to position the implant 2 mm recessed relative to the articular surface based on MRI, radiograph, or arthroscopy	■ pts. with >2 defects, 2 corresponding defects or bilateral defects, ■ osteoarthritis, ■ bone lesions deeper than 0.7 cm, ■ axis deviation of more than ±5° in the frontal plane, ■ unresolved knee instability, ■ rheumatoid arthritis, ■ infectious diseases, ■ endocrine, metabolic or autoimmune diseases, ■ previous subtotal or total meniscus resection or mosaicplasty, ■ treatment with cartilage specific medication (e.g., hyaluronic acid), ■ chondropathia patellae, patella dysplasia or patella instability, ■ concomitant lesions of anterior cruciate ligament, meniscus or axial malalignement.		■ inflammatory joint disease ■ serious illness ■ alcohol or drug abuse during the past 3 yrs ■ malalignment ■ symptomatic ligament instability
Primary endpoint(s)	Overall KOOS preoperative until 5 yrs postoperatively	Clinical evaluation as well as MRI evaluation at 6,12,24 and 60 months		Change in the KOOS score
Secondary endpoint(s)	Confirmatory: KOOS Pain KOOS Quality of Life KOOS Activities of Daily Living Responder rate Nonconfirmatory: IKDC, MRI	Change from Baseline in the patient's evaluation of overall knee condition (Modified Cincinnati Knee Rating Scale Change from Baseline in the patient's evaluation of pain using the VAS Change from Baseline in the patient's evaluation of overall knee condition using the ICRS Adverse Events		Treatment failure[29] Change from baseline in KOOS subscales Lysholm score VAS pain score
Prior surgery, n (%)	Previous ACL reconstruction: 13 (7.8) vs. 7 (8.3) Previous Meniscectomy: 36 (21.6) vs. 22 (22.6) Concomitant meniscectomy 50 (29.9) vs. 19 (22.6)	8 (47.1*) | 10 (58.8*) vs. 6 (46.2*)		Number of previous surgical procedures in the same knee: 1: 3 (15.0) vs. 6 (28.6) 2: 10 (50.0) vs. 6 (28.6) 3: 6 (30.0) vs. 7 (33.3) 4: 0 (0.0) vs. 1 (4.8) 5: 0 (0.0) vs. 0 (0.0) 6: 1 (5.0) vs. 1 (4.8)

[29] Treatment failures were reported as either a "hard failure" or a "clinical failure." A hard failure was defined as the patients needing a new resurfacing procedure of the index lesion or implantation of a knee prosthesis. A clinical failure was defined as any deterioration in KOOS scores at 2-year follow-up compared with baseline. Diagnostic re-arthroscopy or arthroscopy with debridement of synovia or the defect was not considered a failure.

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
Prior surgery, n (%) *(continuation)*				Microfracture: 10 (50.0) vs. 11 (52.4) ACL reconstruction: 2 (10.0) vs. 2 (9.5)
Age of patients, mean, yrs (SD/range)	42 (±11.2) vs. 46 (±11.2)	39 (±9.0) | 34 (±11.0) vs. 40 (±6.0)		Mean (SD), range: 38.3 (±8.2), 24-55 vs. 37.2 (±10.8), 19-55
Postoperative treatment(s)	Staged rehabilitation program (all pts.): limited partial weightbearing for 4 weeks, increasing partial weightbearing to reach full weightbearing after 6 weeks. Cryotherapy during the first 48 hours, continuous passive motion for 3 weeks; quadriceps isometric sets, electrostimulation immediately; stationary cycling at 4 weeks. Hydrotherapy after 2 months; resistance muscle-strengthening exercises after 3 months allowed, as well as outdoor cycling activity and skiing after 6 months.	Staged rehabilitation program (all pts.): increasing weight bearing (full weight bearing 7-12 weeks after surgery) and mobilisation exercises, electrotherapy of leg muscles, proprioception, full weightbearing at 7-12 weeks postoperatively. Aquatraining allowed up to 3 weeks, swimming 3-6 weeks after surgery, biking 7-12 weeks, jogging after 9-12 months, contact sport after 18 months.		Staged rehabilitation program (all pts.): continuous passive motion at hospital; partial weightbearing (15-20kg) for the first 6 weeks; restricting movement for 6 weeks for patients with defects in the patellofemoral joint; indoor cycling as soon as the pain and swelling allowed it. At 6 weeks evaluation by a physical therapist.
Follow-up (months)	24[30]	120 months		24 months (120 months planned)
Loss to follow-up, n (%)	At 24 months: 4 (2.4) vs. 4 (4.8)	Primary Analysis, up to 5 yrs FU: Long-term follow up (up to 10 yrs)		At 24 months: 3 (15.0*)[31] vs 0 (0.0)
		At 60 months:1 (5.9*) | 3 (17.6*) vs. 4 (30.8*)	No further loss to follow up, however MRI data was only available for: 32 (9 | 14 vs. 9)	
BMI, mean, kg/m²	26.4 (±4.2) vs. 27.9 (±3.8)	27.4 (±4.4) | 27.6 (±4.0) vs. 25.0 (±2.9)		27.9 (±4.3) vs. 25.7 (±4.3)
Defect size, mean, cm² (SD)	N pts (%) > 3 cm² 98 (58.7) vs. 41 (48.8) ≤3 cm² 69 (41.3) vs. 43 (51.2)	3.9 (±1.1) | 3.8 (±2.1) vs. 2.9 (±0.8)		mean (SD), range 5.2 (±2.4), 2.0-12.3 vs. 4.9 (±4.4), 1.2-21.5
Location of lesion, n (%)	NR	Cartilage defect (NR)		Medial femoral condyle: 7 (35.0) vs. 7 (33.3) Lateral femoral condyle: 1 (5.0) vs. 2 (9.5) Trochlea: 5 (25.0) vs. 7 (33.3) Patella: 4 (20.0) vs. 1 (4.8) Trochlea and patella: 2 (10.0) vs. 2 (9.5) Trochlea and medial femoral condyle: 1 (5.0) vs. 2 (9.5)
Clinical classificationn, n (%)	Kellgren-Lawrence grade of OA None: 0 or 1: 91 (54.5) vs. 30 (35.7) Mild/ moderate: 2 or 3: 76 (45.5) vs. 54 (64.3) ICRS 4b: 63 (37.7) vs. 16 (19) ICRS 3 and 4a: 104 (62.3) vs. 68 (81)	Clinical evaluation as well as MRI evaluation at one, two and five years follow-up		Kellgren-Lawrence Score: 0: 4 (20.0) vs. 7 (33.3) 1: 8 (40.0) vs. 9 (42.9) 2: 8 (40.0) vs. 2 (9.5) 3: 0 (0.0) vs. 3 (14.3)

[30] 60 months planned.

[31] One described as lost to follow up, 2 as hard failures (patients needing a new resurfacing procedure; they were not excluded from analysis).

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
Clinical classificationn, n (%) *(continuation)*				ICRS grade- main defect: 3: 17 (85.0) vs. 16 (76.2) 4: 3 (15.0) vs. 5 (23.8) ICRS grade- secondary defect: 3: 4 (100) vs. 2 (50.0) 4: 0 (0.0) vs. 2 (50.0)
Outcomes				
Efficacy				
Physical function, activity (e.g. KOOS, Lysholm score, TAS, IKDC), mean (± SD)				
KOOS mean (SD)	**Overall:** *mean difference, 95% CI, p-value* **Baseline:** 0.5 (3.9-2.9) **At 6 months:** 8.2 (3.3-13.0), **p=0.001** **At 12 months:** 12.5 (7.3-17.9), **p<0.0001** **At 18 months:** 18.3 (13.0-23.5), **p<0.0001** **At 24 months:** 22.5 (17.0-28.0), **p<0.0001** The posterior probability of superiority for all 4 confirmatory secondary endpoints was 1.00. As this value was greater than the prespecified Bayesian posterior probability of 0.975, it was concluded that the implant was superior to the SSOC in the improvement from baseline to 24 months in all of the secondary endpoints as well.	NR	NR	mean (SD) Baseline: 54.1 (±19.2) vs. 58.5 (±15.7) Mean (range)** Baseline: 54.1 (45.1-63,1) vs. 58.5 (51.3-65.8) At 12 months: 69.1 (60.5-78.1) vs. 68.2 (61.6-76.3), p=0.02 (in favor of CG) At 24 months: 72.2 (64.0-79.9) vs. 68.8 (61.4-76.5) mean delta between groups at 24 months: 18.1 vs. 10.3, p=0.17 Subscales: at 24 months the mean difference was higher in the AMIC group, but the difference was not statistically significant (lowest p-value was for KOOS Sport/rec (22.0 vs. 8.6, **p=0.08**)
IKDC mean (SD) *Higher scores indicate better function*	MCID: 16.7 at 12 months after articular cartilage repair surgery[32] IG (CG was not reported) change from baseline At 6 months: 24.0 (±18.8) At 12 months: 32.5 (±20.6) At 18 months: 38.1 (±20.8) At 24 months: 43.0 (±21.2) Intergroup difference, mean (95% CI) At 12 months: 12.0 (6.5-17.5) At 16 months: 16.3 (10.7-21.9) At 24 months: 22.7 (16.8-28.6) **p<0.001** at all time points	NR	NR	NR
WOMAC mean (%/SD) *Lower socres indicate better function*	NR	NR	NR	NR

[32] Reported by Altschuler, information available from Roos [104].

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
Modified Cincinnati Knee total score *Higher scores indicate better function*	NR	**Baseline33**: 48 (±15) | 45 (±19) vs. 38 (±19) **At 12 months:** 67 (±26) (p=0.028) | 82 (±15) (p< 0.001) vs. 72 (±18) (**p<0.001**), *Change after 12 months:* +37* | +19* vs. +34* **At 24 months**: 85 (±18) | NR vs. 74 (±26) *Change after 24 months:* NR | +37* vs. +36* **At 60 months**: values NR stable or improving in both AMIC groups, whereas a **significant** decrease was observed in the MFx group (p=0.002 AMIC glued, p=0.01 AMIC sutured).	**At 120 months:** 84.3 (±17.1) | 81.6 (±21.2) vs. 56.1 (±18.6), **p <0.05** MD 26.9 (95%CI 14.8;38.9)*	NR
Lysholm Score mean (%/SD)	NR	NR	NR	Baseline: 50.5 (±18.2) vs. 52.6 (±11.6) mean delta between groups: 19.7 vs. 17.0, p=0.66 mean (95% CI) Baseline: 50.0 (41.7-59.2) vs. 52.6 (47.3-57.8) At 12 months: 67.2 (58.6-75.8) vs. 64.7 (57.3-72.1) At 24 months: 70.1 (61.0-79.6) vs. 69.6 (62.2 -. 76.9)
TAS mean (range) *Higher scores indicate improved ADL*	NR	NR	NR	NR
ICRS mean (SD)	NR	**Baseline**: 46 (±20) | 54 (±19) vs. 57 (±22) **12 months**: 15 (±13) (**p<0.001**) |16 (±15) (p<0.001) vs. 15 (±17) (**p<0.001**) *Change after 12 months:* -31.0* | -38.0* vs. -42.0* **60 months**: NR both AMIC groups still reported very low pain, whereas pain increased non-significantly in the MFx group.	NR	NR

[33] Baseline values are based on whole study sample, whereas changes from baseline are calculated based on the sample that remained at follow-up, only.

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: physical functioning (PF), physical role (PR), vitality (VI) mean (SD) *Higher scores indicate better function*	NR	NR	NR	NR
Pain				
VAS mean (SD) *Lower scores indicate less pain*	NR	NR	**Baseline:** 46 ± 20 | 54 ± 19 vs 57 ± 22 **At 60 months:** 11 (±20) | 15 (±22) vs 30 (±19) **At 120 months:** 12 (±21) | 11 (±16) vs 31 (±20), NS	Baseline: 57.6 (±20.6) vs. 50.0 (±20.1) mean (95%CI) Baseline (57.6 (47.8-67.0) vs. 50.0 (40.9-59.0) At 12 months: 29.4 (17.2-41.6) vs. 27.2 (19.1-35.5) At 24 months: 27.0 (17.1-37.0) vs. 30.4 (20.1-41.2) mean delta at 24 months: 30.6 vs. 19.6, p=0.19
KOOS pain mean (SD)	mean**: Baseline: 46.5 vs. 49.7 At 6 months: 78.8 vs. 70.2 At 12 months: 83.2 vs. 70.0 At 18 months: 87.5 vs. 68.7 At 24 months: 89.5 vs. 69.1	NR	NR	Values NR Subscales: at 24 months the mean difference was higher in the AMIC group, but the difference was not statistically significant
WOMAC Pain subscale mean (%/SD) *Lower scores indicate less pain*	NR	NR	NR	NR
Quality of life				
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: emotional role (ER), psychological well-being (PS) mean (SD) *Higher scores indicate better QoL*	NR	NR	NR	NR

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
KOOS QoL *Subscale, higher scores indicate better QoL*	mean** Baseline: 25.6 vs. 26.9 At 6 months: 52.2 vs. 43.9 At 12 months: 61.7 vs. 49.0 At 18 months: 68.4 vs. 49.0 At 24 months: 73.9 vs. 48.8 The posterior probability of superiority for all 4 confirmatory secondary endpoints was 1.00. As this value was greater than the prespecified Bayesian posterior probability of 0.975, it was concluded that the implant was superior to the SSOC in the improvement from baseline to 24 months			
Structural repair				
MR Imaging	**At 12 months:** overall difference between groups s.s. (**p=0.0001**) **At 24 months:** 88.5% of those treated with the scaffold had ≥75% defect fill as opposed to only 30.9% among those treated with SSOC (**p<.0001**) 1.3% of the implant group had <50% defect fill at 24 months versus approximately 50% in the SSOC group	**At 12 months:** 35-50% of the pts. had a defect filling of two-thirds or more. **At 24 months:** defect filling was more complete in the AMIC groups, where at least 60% of the pts. had a defect filling of more than two-thirds compared to only 25% of the pts. in the MFx group. **At 60 months:** defect filling was the lowest in the MFx group, versus both AMIC groups.	At 120 months Data available only for 32 patients (86%) Effusion was lower in AMIC-treated patients (data not shown). Changes in subchondral bone: comparable proportions of patients in each group showed evidence of changes	NR
MOCART Score *Higher scores indicate more complete defect filling*	NR	NR	**At 120 months:** 34.4 (±23.2) | 31.0 (±20.3) vs 37.7 (± 29.3), n.s. (p=0.879) MD -5 (95%CI-25.7;15.7)*	NR
Necessity of total joint replacement	NR	1 (5.9*) | 0 (0.0) vs. 0 (0.0)	NR	NR
Safety				
Complications/adverse events, n (%)	≥1 AE in 98 (58.7) vs. 65 (77.4) patients Increased transient knee pain following surgery: 15.0% vs. 39.3% Increased swelling or effusion: 5.4% vs. 4.8%	13 adverse events in 9 pts.	NR	NR
Serious adverse events, n (%)	≥1 serious AE: 26 (15.6) vs. 17 (20.2) Wound complications requiring antibiotics and prolonged wound dressing: 2 (1.2) vs. 1 (1.2) Septic arthritis requiring implant removal, surgical debridement, and antibiotic therapy: 1 (0.6) vs. NR	0 (0.0) vs. 0 (0.0)	**At 120 months**: no serious AE related to the treatment was reported for any patient	0 (0.0) vs. 0 (0.0) No major acute complications, such as deep infection, venous thrombosis, or cardiovascular events, were observed in any of the groups.

Author, year	Altschuler et al. 2023 [45]	Anders et al. 2013 [44] Volz et al. 2017 (primary analysis up to 5 yrs [88])[25]	Volz 2024 (10 yrs follow-up [89])	Fossum et al. 2019 [49]
Serious adverse events, n (%) *(continuation)*	Decreased range of motion versus baseline 2 (1.2) vs. NR Persistent muscle atrophy NR vs. 4 (4.8) Deep venous thrombosis 1 (0.6) vs. 1 (1.2)			
Procedure-related adverse event, n (%)	23 (13.8) vs. 23 (27.4)	0 (0.0) vs. 0 (0.0)	NR	NR
Device-related adverse events, n (%)	5 (3.0) vs. NA	NR	NR	NR
Re-operation rate, n (%)	Revision surgery: 0 (0.0) vs. 4 (4.8) Treatment failures in patients[34]: 12 (7.2) vs. 18 (21.4), p=0.002 mild to moderate OA: (5.3) vs. (27.8) larger lesions: (5.1) vs. (22.0)	**12 months:** 1 (5.9*) | 0 (0.0) vs. 1 (7.7*) **24 months:** 1 (5.9*) | 0 (0.0) vs. 2 (15.4*)	**At 120 months,** no further revision surgery was observed	At 24 months: rearthroscopy: 3 (14.3*) vs. 3 (15.0*) 2 reoperations: 1 (4.8*) vs. 1 (5.0*)
Procedure related mortality n (%)	0 (0.0) vs. 0 (0.0)	NR	NR	NR

Abbreviations: ACI … autologous chondrocyte implantation; ACL … anterior cruciate ligament; ADL … activities of daily living; AE … adverse event; AMIC … autologous matrix-induced chondrogenesis; BMI … body mass index; CG … control group; CI … confidence interval; FU … follow-up; ICRS … International Cartilage Repair Society; IG … intervention group; IKDC … International Knee Documentation Committee; KL … Kellgren-Lawrence; KOOS … Knee Injury and Osteoarthritis Outcome Score; MCID … minimal clinically important difference; MD … mean difference; MFx … microfracture; MOCART … magnetic resonance observation of cartilage repair tissue; MRI … magnetic resonance imaging; n.s. … not significant; NCT … national clinical trial; NR … not reported; OA … osteoarthritis; pts … patients; QoL … quality of life; RCT … randomised controlled trial; s.s. … statistically significant; SD … standard deviation; SF … Short Form (Health Survey); SSOC … standard of care; VAS … Visual Analogue Scale; vs. … versus; WOMAC … Western Ontario and McMaster Universities Osteoarthritis Index; yrs … years

Notes:

** Self-calculated*

*** Numbers estimated by using the webplotdigitizer[103].*

[34] Were defined as any secondary invasive intervention in the treated joint (e.g., open, mini-open surgical or arthroscopic procedures as well as any intraarticular injection).

Table A-3: One-stage matrix assisted cartilage repair: Results from randomised controlled trials

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
Trial registry number	**EUCTR2011-003594-28-DE**	**NCT02539030**	**NCT01282034**	**NCT00314236**
Country	Germany	South Korea	Italy, Sweden, Belgium, Switzerland, Austria, Germany, Norway, Poland, South Africa	Canada, Spain, South Korea
Sponsor	BioTissue AG, Switzerland	Sewon Cellontech research grant (grant ID: 03CAR)	Fin-Ceramica Faenza S.p.A., Italy	BioSyntech Canada Inc., Piramal Life Sciences
Intervention/ Product	Matrix-augmented bone marrow stimulation/Chondrotissue, BioTissue AG: debridement, perforation, and implantation of chondrotissue	Porcine-derived collagen-augmented chondrogenesis/CartiFill,; Sewon Cellontech, Seaoul, Korea/Greenplast; Green Cross, Yongin, Korea), micro-facture, debridement, collagen implant with Cartifill and Thrombin mixture, as well as fibrinogen was applied.	AMIC/MaioRegen™, Fin-Ceramica Faenza S.p.A., Italy: Arthrotomy, nanostructured collagen-hydroxyapatite (coll-HA) multilayer scaffold (osteochondral biomimetic scaffold), defect preparation, implantation of the scaffold	AMIC/BST-CarGel®, Piramal Life Sciences, Bio-Orthopaedic Division): Arthroscopy + miniarthrotomy, one-stage cartilage repair + microfracture/BST-CarGel®
Comparator	MFx alone (debdridement of the femoral cartilage defect, perforation with an arthroscopic awl	MFx alone (microfracturing with awls, debdridement of the margins	MFx alone (arthroscopic perforation of the subchondral bone). In larger lesions (more than 4cm2) ur with a higher damage, with a Kirschner wire, in order to reach the proper depth)	Arthroscopic MFx alone
Study design	Multicentre randomised controlled trial	Multicentre randomised controlled trial	Multicentre randomised controlled trial (RCT)	Multicentre randomised controlled trial (RCT)
Study duration	2009-2015	2013-2016	2011-2015	2006-2015
Blinding	Single blinded (pts)	None (open-label)	Patients and surgeons were not blinded. (statistician was blinded)	Single-blinded (investigators and patients were not blinded, but there was an independent centre that carried out the analysis
Number of pts at randomisation	30 (15 vs. 15)	100 (52 vs. 48)	124 (61 vs. 63)	80 (41 vs. 39)[35]
Female, n (%)	6 (50.0*) vs. 3 (25.0*)	33 (73.3*) vs. 35 (79.6*)	15 (29.4*) vs. 18 (36.7*)	18 (43.9*) vs. 14 (35.9*)
Inclusion criteria	■ aged 18-68 yrs ■ with MFx indication, attributed to a focal cartilage defect of 0.5 to 3 cm^2 in weight-bearing areas of the femoral condyles	■ aged 15 to 65 yrs ■ presence of cartilage defect (knee osteoarthritis or knee traumatic arthritis) ■ misalignment of the tibia and femur, or treatment for such misalignment	■ Patients aged between 18 and 60 years; ■ Knee symptomatic chondral lesion of grade III/IV (according to Outerbridge Classification) or osteochondral lesion; ■ Not re-fixable OCD lesions; ■ Lesion between 2-9 cm^2; ■ Single lesion;	■ aged 18-55 yrs, ■ single, focal cartilage lesion on the femoral condyle, ■ moderate knee pain (>4 on a 10 point VAS).

[35] Data extracted from Stanish [92] only 60 (34 vs. 26) available after 5 yrs.

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
Inclusion criteria *(continuation)*			■ Patients agreed to actively participate in the rehabilitation protocol and follow-up program; ■ Male or female patients; ■ Women of childbearing age had to use a proven method to prevent pregnancy, before the surgical treatment.	
Exclusion criteria	■ osteochondral defects, general osteoarthritis (≥2 compartments) ■ defect of the patellofemoral joint, tibial defect >2 Outerbridge classification, varus and valgus (>5°), joint stiffness (flexion <90°), ligamentary laxity or lesion, meniscal lesions with more than one-third partial resection or adjacent to the symptomatic cartilage defect ■ history of cartilage surgery (osteochondral transplantation, autologous chondrocyte transplantation, matrix-enhanced autologous chondrocyte implantation) ■ history of MFx in the symptomatic defect or knee surgery (anterior cruciate ligament or meniscal surgery, osteotomy) in previous 6 months ■ allergic reactions to polyglycolic acid or hyaluronan, chemotherapy or radiotherapy in past 3 weeks, ■ rheumatoid arthritis or Bechterew disease, obesity (BMI >30) ■ pregnancy, lactation	■ history of the patient or families having an autoimmune disease or an anaphylactic reaction ■ sensitivity to transplants and/or porcine protein ■ currently pregnant or lactating ■ contraindication to use of a fibrin sealant ■ or previous ligament surgery	■ Patients incapable to understanding and will; ■ Patients participating in previous, concurrent or not, trials (ongoing or completed within 3 months); ■ Patients surgically treated for the same defect within one year; ■ Known allergy to collagen or calcium-phosphates; ■ Patients affected by malignancy; ■ Patients affected by metabolic or thyroid disorders; ■ Patients used to alcohol or drug (medication) abuse; ■ Patients affected by advanced osteo-arthritis (Kellgren-Lawrence grade ≥3); ■ Patients affected by synovitis; ■ Untreated patellofemoral malalignment; ■ Varus or valgus malalignment exceeding 5°; ■ Body Mass Index > 30; ■ Patients previously treated for total or partial meniscectomy (>50% of the meniscus dimension); ■ Multiple lesions; ■ Kissing lesions; ■ Chondral/osteochondral tibial plate defects; ■ Concomitant menisci and chondral/ osteochondral defects to be treated; ■ Untreated knee ligament instability.	■ pts. with multiple lesions or kissing lesions, ■ clinically relevant compartment malalignment (>5 degrees), ■ pts. who underwent ligament treatments in the affected knee within two years prior to trial, ■ inflammatory arthropathy, such as rheumatoid arthritis, systemic lupus, or active gout, ■ previous surgical cartilage treatments in the affected knee in the last 12 months.
Primary endpoint(s)	Defect filling (MRI)	Pain (VAS)	■ IKDC subjective score	■ repair cartilage quantity defined by the degree of lesion filling and the quality of the new repair cartilage at twelve months

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
Secondary endpoint(s)	VAS (pain), KOOS, IKDC, SF-36	Defect filling, KOOS, IKDC	■ KOOS, IKDC, Knee Examination Form, Tegner, VAS Pain Score ■ Tissue regeneration (MRI MOCART scoring system	■ demonstrate that the clinical benefit at twelve months was at least comparable l both treatment groups
Prior surgery, n (%)	NR	13 (28.9) vs. 9 (20.5)	27 (52.9) vs. 23 (46.9)	NR
Age of patients, mean, yrs (SD)	mean (range) 47.9 (35-68) vs. 36.7 (18-51), **p=0.017**	mean (SD, range) 48.9 (±10.2, 22-65) vs. 51.8 (±8.1, 24-63)	34.0 (±10.9) vs. 35.2 (±10.2)	35.1 (±9.6) vs. 37.2 (±10.6)
Postoperative treatment(s)	Staged rehabilitation program (all pts): early mobilisation without weightbearing in the first 6 weeks, limitied flexion until the 6th week. Two weeks after surgery: swimming and aqua gymnastics were permitted. Cycling allowed after 6 weeks, running after 6 months, retrun to contact sports after 18 months	Staged rehabilitation program (range-of-motion exercises, weight bearing ambulation until full weightbearing at 6 weeks post operatively (all pts)	Early isometric and isotonic exercises and electrical neuromuscular stimulation partial weight-bearing by 4th week, progressing to full weight bearing. Swimming and cycling allowed 1 month after surgery. Low active functional training after 4-6 months and joint impact activities after 1 year	Physiotherapy/rehabilitation (all pts.): 12 week program: six weeks non-weight-bearing, progressed to 100% at eight weeks and assisted passive motion manually applied during frequent physiotherapy sessions. No full-impact activities involving jumping or pivoting were permitted for twelve months.
Follow-up (months)	Approx. 24 months (reported as 108 weeks)	24 months	24	60
Loss to follow-up, n (%)	3/15 (20.0*) vs. 3/15 (20.0*)r	At 24 months FU: 7/52 (13.5)) vs. 4/48 (8.3)	At 24 months FU: 6/61 (9.8*) vs. 12/63 (19.1*)	At 12 months: 0 (0) vs. 2 (5) At 60 months: 8 (20.0) vs. 13 (33.3)[36]
BMI, mean, kg/m²	mean (range) 25.1 (22.1-29.6) vs. 24.7 (22.2-29.1)	mean (SD, range) 25.01 (±3.0, 20-33.6) vs. 26.0 (±3.7, 18.0-37.2)	25.6 (± 3.3) vs. 25.2 (± 3.2)	27.0 (±3.3) vs. 25.2 (±3.0)
Defect size, mean, cm² (SD)	1.7 (NR) vs. 1.7 (NR)	mean (SD, range) 4.0 (±1.9 (1.5-9.4) vs. 4.7 (±2.5, 1.1-12.8)	3.4 (± 1.5) vs. 3.5 (± 1.6)	2.3 (±1.4) vs. 1.9 (±1.4)
Location of lesion, n (%)	NR	NR	Chondral and osteochondral lesions: Condyle: 37 (72.6) vs. 23 (47.0) Trochlea: 2 (3.9) vs. 6 (12.2) Patella: 12 (23.5) vs. 20 (40.8)	Femoral condyle cartilage lesion[37]: Medial femoral condyle: 40 (97.6) vs. 38 (97.4) Lateral femoral condyle: 1 (2.4) vs. 1 (2.6)
Clinical classification, n (%)	ICRS 3: 10 (83.3*) vs. 8 (66.7*) 4: 2 (16.7*) vs. 4 (33.3*)	Traumatic Arthritis: 4 (8.9) vs. 5 (11.4) Osteoarthritis: 41 (91.1) vs. 39 (88.6) Kellgren-Lawrence grade in OA: 1: 10 (22.2) vs. 5 (11.4) 2: 16 (35.6) vs. 18 (40.9) 3: 12 (26.7) vs. 14 (31.8) 4: 3 (6.7) vs. 2 (4.6) ICRS: 3: 12 (26.7) vs. 11 (25.0) 4: 33 (73.3) vs. 33 (75.0)	NR	NR

[36] Loss to follow-up for assessing joint functionality by WOMAC score.

[37] Extracted from Stanish [92].

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
Outcomes				
Efficacy				
Physical function, activity (e.g. KOOS, Lysholm score, TAS, IKDC), mean (± SD)				
KOOS mean (SD)	**KOOS symptoms** **mean (SD)** **Baseline:** 50.0 (±15.8) vs. 71.1 (±14.6), **p=0.003** *median (IQR; 95%CI)* **Baseline:** 57.2 (38.6-60.5; 18.0-71.2) vs. 66.1 (63.1-81.1; 45.9-96.5)** **At 12 weeks:** 75.3 (62.4-82.1; 46.3-89.1) vs. 80.3 (65.9-93.0; 42.7-99.8)** **At 54 weeks (approx. 12 months):** 83.9 (52.0-91.4; 42.7-99.8) vs. 87.8 (73.3-93.3; 60.4-99.8)** **At 108 weeks (approx. 24 months):** 85.7 (79.6-88.7; 65.8-99.8) vs. 89.5 (85.5-93.3; 75.1-96.5)** Significant differences in change from baseline only within the intervention group after 54 and 108 weeks **(p<0.05)** **KOOS ADLs** *mean (SD)* **Baseline:** 53.0 (±18.8) vs. 78.2 (±18.9), **p=0.003** *median (IQR; 95%CI)* **Baseline:** 46.1 (38.1-69.4; 32.2-88.2) vs. 87.8 (68.6-91.8; 43.9-97.0)** **At 12 weeks:** 78.9 (69.4-91.6; 56.0-99.8) vs. 87.5 (74.6-93.5; 46.2-99.8)** **At 54 weeks (approx. 12 months):** 95.0 (89.8-97.1; 79.4-99.8) vs. 96.0 (92.3-99.9; 82.1-99.9)** **At 108 weeks (approx. 24 months):** 95.0 (89.3-96.8; 78.5-99.9) vs. 99.3 (96.0-99.9; 89.0-99.9)** Significant differences only within groups at 12 weeks (IG), 54 and 108 weeks (IG and CG), **p<0.05** **KOOS Sport/rec** *mean (SD)* **Baseline:** 31.7 (±27.7) vs. 43.8 (±13.8), **p=0.004** *median (IQR; 95%CI)* **Baseline:** 24.8 (15.0-36.3; 0.3-67.8) vs. 40.2 (34.7-51.2; 24.5-69.6)** **At 12 weeks:** 60.1 (27.3-71.4; 7.8-95.0) vs. 72.3 (49.9-89.5; 0.2-99.8)** **At 54 weeks (approx. 12 months):** 70.1 (55.1-99.8; 14.8-99.8) vs. 80.1 (66.4-97.8; 39.7-99.9)**	**KOOS total:** **Baseline:** 53.7 (±18.8) vs. 54.9 (±18.2), *p*=0.7635 **At 12 months:** 69.7 (±16.4) vs. 70.3 (±17.6), *p*=0.9509 **At 24 months:** 77.1 (±14.1) vs. 75.2 (±15.5), *p*=0.6906 MD 1.9 (95%CI -3.9;7.7)* Statistical significant differences only within groups from baseline to FU; no s.s. differences between groups for subscales	**mean** **KOOS Symptom:** **Baseline:** 60.8 vs. 60.3 **At 24 months:** 76.7 vs. 77.3 **mean change*:** 15.9 vs. 17.0 **KOOS ADL** **Baseline:** 67.6 vs. 63.2 **At 24 months:** 83.8 vs. 84.7 **mean change*:** 16.2 vs. 21.5 **KOOS Sport/rec** **Baseline:** 30.1 vs. 28.7 **At 24 months:** 57.3 vs. 58.4 **mean change*:** 27.2 vs. 29.7 There was no statistically significant difference from baseline to 2-year follow-up	NR

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
KOOS mean (SD) *(continuation)*	**At 108 weeks (approx. 24 months):** 92.5 (75.3-92.5; 55.1-99.8) vs. 85.0 (54.9-100.0; 35.0-100.0)** There was significant improvement after 54 and 108 weeks in both groups but not between groups (**p<0.05**)			
IKDC mean (SD) *Higher scores indicate better function*	Baseline: 38.0 (±10.4) vs. 47.8 (±15.6), p=0.28 At 12 weeks: 50.4 (±19.2) vs. 77.9 (±19.8)** At 54 weeks (approx. 12 months): 67.8 (±17.6) vs. 72.3 (±9.9)** At approx. 24 months (108 weeks) 75.4 (±14.2) vs. 73.3 (±13.9) n.s. (p-value NR)** IKDC scores were significant within groups after 54 and 108 weeks (**p<0.05**), not between groups)	Total: Baseline: 43.8 (±19.7) vs. 47.6 (±17.9), p=0.3323 At 12 months: 65.8 (±19.3) vs. 65.8 (±21.2), p=0.9981 At 24 months: 70.3 (±18.5) vs. 71.2 (±19.9), p=0.6281 Statistical significant differences only within groups from baseline to FU; no s.s. differences between groups for subscales	**Subjective IKDC:** **Baseline:** 43.2 (±16.6) vs. 41.1 (±15.9) **12 months**: 60.7 (±17.3) vs. 61.8 (±18.0) *Change after 12 months:* +17.5* vs. +20.7* **24 months**: 66.7 (±21.0) vs. 63.6 (±18.2), n.s., p=NA *Change after 24 months:* +23.5* vs. +22.5* There was no statistically significant difference from baseline to 2-year follow-up	NR
WOMAC mean (%/SD) *Lower socres indicate better function*	NR	NR	NR	**WOMAC stiffness subscale** **Baseline**[38]**:** 10.5 (±4.4) vs. 9.4 (±4.9), n.s. (p=0.224) *Mean (±SE)* **Change after 12 months**[37]**:** -5.9 (±0.7) vs. -6.6 (±0.71), n.s (p=0.543)) MD 0.7 (95%CI -1.3;2.7) **Change after 60 months:** -5.6 (±0.7) vs. -6.7 (±0.6), n.s. (p=0.236) MD 1.1 (95%CI -0.7;2.9) **WOMAC physical function subscale** **Baseline**[38]**:** 80.3 (±38.5) vs. 75.9 (±38), n.s. (p=0.721) *Mean (±SE)* **Change after 12 months:** -55.9 (±4.24) vs. -60.6 (±4.4), n.s. (p=0.443) MD 4.7 (95%CI -7.22;16.62) **Change after 60 months:** -56.5 (±4.6) vs. -62.1 (±3.4), n.s. (p=0.326) MD 5.6 (95%CI-5.7;16.8)
Modified Cincinnati Knee total score *Higher scores indicate better function*	**NR**	**NR**	**NR**	**NR**

[38] Scores had a maximum value of 50 for Pain, 20 for Stiffness, and 170 for Function.

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
Lysholm Score mean (%/SD)	**NR**	**NR**	**NR**	**NR**
TAS mean (range) *Higher scores indicate improved ADL*	**NR**	**NR**	**Baseline: 3.0 (0.0-7.0) vs. 3.0 (0.0-9.0)** **12 months: 4.0 (2.0-7.0) vs. 4.0 (1.0-9.0)** **Change after 12 months: +1.0* vs. +1.0*** **24 months: 4.0 (1.0-9.0) vs. 4.0 (2.0-8.0)** **Change after 24 months: +1.0* vs. +1.0*** **There was no statistically significant difference from baseline to 2-year follow-up**	**NR**
ICRS mean (SD)	**NR**	**NR**	**NR**	**NR**
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: physical functioning (PF), physical role (PR), vitality (VI) mean (SD) *Higher scores indicate better function*	**There was no significant difference in SF-36 outcome (general health condition) between treatment groups.**	**NR**	**NR**	**SF-36 v2 physical component:** **Baseline: NR** **Change after 12 months[37]:** **+13.0 (±1.5) vs. +14.8 (±1.5), n.s. (p=0.416)** **MD -1.8 (95%CI -5.9;2.3** **Change after 60 months:** **+13.1 (±1.6) vs. +14.5 (±1.4), n.s. (0.478)** **MD -1.4 (95%CI -5.7;2.8)**
Pain				
VAS mean (SD) *Lower scores indicate less pain*	**Baseline:** 4.8 (±2.7) vs. 2.4 (±2.0) **At 6 weeks:** 1.0 (±0.8) vs. 2.5 (±0.7)** **At 12 weeks:** 0.9 (±0.9) vs. 1.7 (±2.5)** **At 54 weeks(approx. 12 months):** 0.8 (±0.6) vs. 1.5 (±1.3)** **At 108 weeks(approx. 24 months):** 0.7 (±0.9) vs. 1.1 (±1.1)** Significant pain relief in comparison with baseline data in the m-BMS group for weeks 6, 12, 54 and 108 (**p<0.05**).	Baseline: 58.2 (±21.8) vs. 55.1 (±26.9), *p*=0.5507 At 12 months: 22.2 (±24.1) vs. 21.0 (±20.7), *p*=0.9443 At 24 months: 15.5 (±21.6) vs. 21.5 (±25.9), *p*=0.4290	**Baseline:** 50.1 (±26.7) vs. 53.1 (±22.7), p=NR **At 12 months**: 23.8 (±20.8) vs. 29.2 (±23.2), p=NR *Change after 12 months:* -26.3* vs. -23.9* **At 24 months**: 26.5 (±27.5) vs. 23.2 (±20.9), p=NR *Change after 24 months:* -23.6* vs. -29.9*	NR
KOOS (pain) mean (SD)	*mean (±SD)* **Baseline:** 41.9 (±17.6) vs. 66.9 (±20.9) *median (IQR, 95%CI)* **Baseline:** 40.4 (24.1-59.2; 21.8-63.5) vs. 72.1 (53.1-81.8; 30.5-91.5)** **At 12 weeks:** 72.1 (62.4-77.1; 40.6-97.3) vs. 79.1 (64.4-95.3; 18.5-99.7)** **At 54 weeks (approx. 12 months):** 89.1 (78.5-96.6; 72.4-99.8) vs. 93.0 (83.8-95.8; 69.3-99.8)**	Baseline: 53.5 (±19.1) vs. 56.2 (±20.5), *p*=0.5175 At 12 months: 74.4 (±16.1) vs. 74.1 (±19.0), *p*=0.8921 At 24 months: 82.2 (±11.6) vs. 77.8 (±16.1), *p*=0.3317 MD 4.4 (95%CI -1.2;9.9)	**KOOS pain:** **Baseline:** 59.4 vs. 57.5 **At 24 months:** 77.6 vs. 79.4 **mean change*:** 18.2 vs. 21.9	NR

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
KOOS (pain) mean (SD) *(continuation)*	**At 108 weeks (approx. 24 months):** 90.3 (82.5-95.2; 63.7-97.5) vs. 91.8 (83.3-99.9; 69.6-99.9)** There was significant improvement over time in both groups concerning the KOOS but not between groups (after 54 and 108 weeks)			
WOMAC Pain subscale mean (%/SD) *Lower scores indicate less pain*	**NR**	**NR**	**NR**	**Baseline38:** **22.4 (±10.3) vs. 22.9 (±9.1), n.s. (p=0.544)** **mean (SE)** **Change after 12 months:** **-16.2 (±1.2) vs. -16.9 (±1.2), n.s. (p=0.646)** **MD 0.7 (95%CI -2.6;4.0)** **Change after 60 months:** **-15.4 (±1.5) vs. -16.6 (±1.2), n.s. (p=0.474)** **MD 2.9 (95%CI -1.5;7.2)**
Quality of life				
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: emotional role (ER), psychological well-being (PS) mean (SD) *Higher scores indicate better QoL*	There was no significant difference in SF-36 outcome (general health condition) between treatment groups.	NR	NR	**SF-36 psychological well-being** **Baseline:** NR **Change after 12 months**: +3.5 (±1.7) vs. +0.8 (±1.6), n.s. (p=0.229) MD 2.7 ((95%CI -1.9;7.3) **Change after 60 months:** +2.7 (±1.3) vs. -0.17 (±1.8), n.s. (p=0.125) MD 2.9 (95%CI -1.5;7.2)
KOOS (QoL) mean (SD)	**KOOS QoL:** **mean (SD)** **Baseline:** 31.3 (±18.3) vs. 39.6 (±14.2), p=0.115 *median (IQR, 95%CI)* **Baseline:** 27.9 (23.4-32.9; 12.3-46.7) vs. 37.4 (29.5-51.4; 19.0-62.1)** **At 12 weeks:** 43.6 (37.5-70.3; 18.9-93.7) vs. 53.1 (37.4-73.3; 24.2-93.8)** **At 54 weeks (approx. 12 months):** 59.7 (43.4-91.4; 12.3-99.8) vs, 65.6 (51.4-79.6; 37.4-99.8)** **At 108 weeks (approx. 24 months):** 62.4 (48.6-71.9; 24.5-99.8) vs. 68.8 (49.9-81.1; 24.5-99.8)** There was significant improvement over time in both groups after 54 (IG and CG) and 108 (IG) weeks but not between groups		**KOOS QoL:** **Baseline:** 27.9 vs. 23.8 **At 24 months:** 54.1 vs. 55.3 **mean change*:** 26.3 vs. 31.5	

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
Structural repair				
MR Imaging (defect filling)	Defect filling, % In terms of defect filling at 12 weeks after surgery, MRI revealed progressive defect filling in both treatment groups, showing >50% of defect filling at postoperative 108 weeks (24 months) Henderson Score: Baseline: 3.3 (±0.8) vs. 2.8 (±0.7), *p*=0.171 delta-score: At 12 weeks: -0.4 (±0.2) vs. -0.3 (±0.3)** At 54 weeks (approx. 12 months): -0.9 (±0.5) vs. -0.8 (±0.3)** At 54 weeks (approx. 24 months): -1.2 (±0.2) vs. -0.8 (±0.2)** No significant differences between groups at each time point. Significant changes in both groups at week 108 (approx. 24 months) compared to 12 weeks after surgery. (p≤0.01) No statistical significant difference between groups at each time point. Changes in overall Henderson score were significantly higher at week 12 and week 108 (approx. 24 months) on the m-BMS group compared with the MF group:(**p<0.01**).	Defect filling, n pts (%) <50%: 5 (6.1) vs. 14 (17.1), **p=0.0377** ≥50%: 37 (45.1) vs. 26 (31.7), p=NR	**See MOCART Score**	**Complete filling of the defect** mean % (SD) **At 12 months:** 92.8 (±2.0) vs. 85.2 (±2.1), **p=0.011** **At 60 months:** 93.79 (±1.16) vs. 86.96 (±2.85), **p=0.017**
MOCART Score *Higher scores indicate more complete defect filling*	NR	Total Score: (available for 45 vs. 42 patients) 50.9 (±19.8) vs. 45.7 (±19.9), *p*=0.2274 MD 5.2 (95%CI -2.6;12.9) Degree of defect repair and filling of the defect: 12.1 (±5.4) vs. 9.6 (±5.2), **p=0.0201**	No total score reported **Complete filling of the defect** (mean% (SD)[39]: **At 6 months**: 53.3 vs. 39.5 **At 12 months**: 40.8 vs. 55.6 **At 24 months**: 49.0 vs. 65.9 n.s. difference in the MRI scores between groups	NR
Necessity of total joint replacement	NR	NR	NR	NR
Safety				
Complications/adverse events, n (%)	Severe effusion: 0 (0.0) vs. 1 (8.3*) Mild swelling: 3 (25.0*) vs 0 (0.0) Restricted range of motion: 2 (16.7*) vs. 0 (0.0) Allergic reactions 0 (0.0) vs. 0 (0.0)	NR	13 (21.0*) vs. 4 (6.5*)[40]	**12 months** (41 vs. 37 pts.)[37]: 40 (98.0)[41] vs. 36 (92.0)[42], n.s. **60 months** (34 vs. 26 pts.): 13 (19.0) vs. 18 (27.0)[43]; p=NR

[39] Scores were calculated on the sample that remained at follow-up only.

[40] Safety was evaluated focusing on number and type of adverse events after surgery in all patients randomised and treated (124 patients); safety population: 62 vs. 62 pts.

[41] Five patients experienced severe adverse events. Most frequent (mild to moderate) events: arthralgia, pain and nausea.

[42] One patient experienced a severe adverse event. Most frequent (mild to moderate) events: arthralgia and pain.

[43] Most frequent event in both groups: pain (11% vs. 17%).

Author, year	Glasbrenner et al. 2020 [90]	Kim et al. 2020 [91]	Kon et al. 2018 [43]	Stanish et al. 2013 [92] & Shive et al. 2015 [93]
Serious adverse events, n (%)	1 (8.3*) vs. 1 (8.3*)	2 (4.4*) vs. 2 (4.6*) urethral caruncle: 1 (2.2*) vs. 0 (0.0) acute hepatoma: 1 (2.2*) vs. 0 (0.0) knee pain and swelling: 0 (0.0) vs. 1 (2.3*) metal removed 0 (0.0) vs. 1 (2.3*)	3 (4.8*) vs. 1 (1.6*)[44] Joint adhesions: 2 vs. 0 Persistent pain: 1 vs. 0 Loose body: 0 vs. 1	**12 months** (41 vs. 37 pts)[37]: 5 (12.2*)[41] vs. 1 (2.7*)[42] **60 months** (34 vs. 26 pts.): 0 (0) vs. 1 (3.8*)[45]
Procedure-related adverse event, n (%)	NR	0 (0*) vs. 0 (0*)	8 (12.9*) vs. 3 (4.8*)[46] Inflammation: 3 vs. 0 Joint adhesions: 1 vs. 0 Persistent pain: 1 vs. 0 Loose body: 0 vs. 0 Joint instability: 0 vs. 1	**12 months** (41 vs. 37 pts.)[37]: 38 (93.0) vs. 30 (77.0)[47]; p=NR **60 months** (34 vs. 26 pts.): 2 (6.0*) vs. 2 (8.0*)[47]; p=NR
Device-related adverse events, n (%)	NR	NR	NR	**12 months** (41 vs. 37 pts.)[37]: 9 (22.0)[48] vs. 0 (0.0), p=NR **60 months** (34 vs. 26 pts.): 1 (3.0*)[47] vs. 0 (0.0); p=NR
Re-operation rate, n (%)	1 (8.3*) vs. 1 (8.3*)	NR	Failures: 2 (3.2*) vs. 0 (0.0) Failure was defined as the need for reintervention on the same defect based on the persistence or recurrence of symptoms.	**60 months** (34 vs. 26 pts.): 0 (0) vs. 1 (3.8*)
Procedure related mortality n (%)	NR	NR	NR	**60 months** 0 (0.0) vs. 0 (0.0)

Abbreviations: ACI … autologous chondrocyte implantation; ACL … anterior cruciate ligament; ADL … activities of daily living; AE … adverse event; AMIC … autologous matrix-induced chondrogenesis; BMI … body mass index; CG … control group; CI … confidence interval; FU … follow-up; ICRS … International Cartilage Repair Society; IG … intervention group; IKDC … International Knee Documentation Committee; IQR … interquartile range; KL … Kellgren-Lawrence; KOOS … Knee Injury and Osteoarthritis Outcome Score; m … months; m-BMS … matrix-augmented bone marrow stimulation; MCID … minimal clinically important difference; MD … mean difference; MFx … microfracture; MOCART … magnetic resonance observation of cartilage repair tissue; MRI … magnetic resonance imaging; n.s. … not significant; NCT … national clinical trial; NR … not reported; OA … osteoarthritis; pts … patients; QoL … quality of life; RCT … randomised controlled trial; s.s. … statistically significant; SD … standard deviation; SE … standard error; SF … Short Form (Health Survey); SSOC … standard of care; TAS … Tegner Activity Scale; VAS … Visual Analogue Scale; vs. … versus; WOMAC … Western Ontario and McMaster Universities Osteoarthritis Index; yrs … years

Note:

** Self-calculated*

*** Numbers estimated by using the webplotdigitizer[103].*

[44] Reported severe adverse events were related to the treatment.

[45] Severe adverse event was not related to the study treatment or index knee but required surgery and radiotherapy.

[46] Reported adverse events were minor early post-operation symptoms.

[47] Kind of complications not stated.

[48] Kind of complications not clearly stated.

Table A-4: One-stage matrix assisted cartilage repair with BMAC: Results from randomised controlled trials

Author, year	De Girolamo et al. 2019 [94]
Trial register number	**n_471/07 (ASL Città di Milano, 21/07 MS) (not available)**
Country	Italy
Sponsor	Funded by Italian Ministry of Health "Ricerca Corrente"
Intervention/Product	AMIC+/ ■ debridement of lesion ■ 24mL bone marrow (ipsilateral iliac crest) added to 6mL of Anticoagulant Citrate Dextrose Solution A (ACD-A). ■ BMAC centrifugation: 3200 rpm for 15 min (room temperature) using MarrowStim™ device (Biomet, USA, currently named "BioCue", Zimmer-Biomet, Warsaw, IN, USA). ■ microfracturing ■ miniarthrotomy approach ■ collagen type I/III bilayer matrix (Chondro-Gide®, Geistlich Pharma AG) dipped into BMAC for 10min, then fixed with synthetic fibrin glue
Comparator	Standard AMIC (debridement of lesion, microfracturing, collagen type I/III bilayer matrix (Chondro-Gide®, Geistlich Pharma AG) positioned and glued.
Study design	Prospective randomised controlled trial (RCT)
Study duration	2007 – 2010
Blinding	non-blinded[49]
Number of pts	24 (12 vs. 12)
Female, n (%)	4 (33.3*) vs. 5 (41.7*), p=ns
Inclusion criteria	■ aged 18-55 yrs ■ one or two grade III or IV articular surface lesions of the knee according to the ICRS (tibiofemoral + patellofemoral joint) ■ lesion size: 2-8 cm^2, and normal surrounding cartilage (accepted one or two grade I/II chondral lesions)
Exclusion criteria	■ ≥ 2 chondral defects ■ immuno-mediated pathologies including osteoarthritis, knee infection, untreatable instability, malalignment or meniscal tears ■ serious cardiologic pathologies ■ problematic general conditions
Primary endpoint(s)	VAS, Lysholm Score until 100 months postoperatively
Secondary endpoint(s)	IKDC objective, TAS until 24 months follow-up (KOOS instead of IKDC at 60- and 100-months follow-up), MRI until 24 months follow-up
Prior surgery, n (%)	3 (25*) vs. 6 (50*), p=ns
Age of patients, mean, yrs (±SD)	30.0 (±11.3) vs. 30.0 (±10.2), p=ns
Postoperative treatment(s)	Staged rehabilitation program: ■ immediate full range of motion, no weight bearing for 3 weeks, full weight bearing after 6 weeks (pts with condylar chondral defect) ■ progressively restore the full range of motion and bearing from the early post-operative days (pts pith patellar defects)
Follow-up (months)	100
Loss to follow-up, n (%)	24 months: 2 (16.7)* vs. 2 (16.7)* > 60 months: 1 (8.33)* vs. 3 (25)*
BMI, mean, kg/m2	NR Weight (kg): 68.8 (±12.9) vs. 69.1 (±11.5), p=ns
Defect size, mean, cm2 (SD)	3.4 (±0.8) vs. 3.8 (±1.0), p=ns
Location of lesion, n (%)	Medial femoral condyle: 6 (50.0*) vs. 7 (58.3*), p=ns Lateral femoral condyle: 2 (16.7*) vs. 3 (35.0*), p=ns Patello-femoral joint: 4 (33.3*) vs. 2 (16.7*), p=ns
Clinical classification, n (%)	Traumatic lesion: 2 (16.7*) vs. 2 (16.7*), p=ns
BMAC concentration factor	MSC concentration factor of 3-fold in the concentrated bone marrow

[49] Patients received a sealed envelope with allocation just before the intervention. Outcome assessors were blinded.

Author, year	De Girolamo et al. 2019 [94]
Outcomes	
Efficacy	
Physical function, activity (e.g. KOOS, Lysholm score, TAS, IKDC), mean (± SD)	
KOOS mean (SD)	**KOOS symptoms**** **Baseline**: NR*** **60 months**: 76.1 (max. 86.0) vs. 67.0 (max. 90.4) **100 months**: 67.1 (max. 86.0) vs. 67.0 (max. 90.4) **KOOS ADLs**** **Baseline**: NR*** **60 months**: 83,8 (max. 88,2) vs. 82.7 (max. 87.4) **100 months**: 78.7 (max. 89.6) vs. 74.0 (max. 87.9) **KOOS Sport/rec**** **Baseline**: NR*** **60 months:** 62.2 (max. 84.9) vs. 49.4 (max. 83.8) **100 months:** 29.7 (max. 84.8) vs. 41.9 (max. 87.2) Satisfactory in both groups in particular for pain and DA, a slight progressive decrease with time for sport and QOL, no differences between groups
IKDC mean (SD) *Higher scores indicate better function*	**IKDC score (A/B/C/D, No %)**[50] **Baseline:** A + B: 67%; C + D: 23% vs. A + B: 84%; C + D: 16% **6 months:** improved vs. improved **12 months:** A improved vs. no further improvement **24 months:** A was significantly increased compared to pre-op ($p < 0.05$); higher percentage of pts. In A compared to B/C/D ($p<0.5$) vs. no significant difference (no counts reported)
WOMAC mean (%/SD) *Lower scores indicate better function*	NR
Modified Cincinnati Knee total score *Higher scores indicate better function*	NR
Lysholm Score mean ±SD (range), p-value	**Baseline**: 65.2 ±16 (33–80) vs. 72.3 ±13.3 (44–89), p=ns **6 months**: 90.4 ±6.6 (80–100), $p < 0.001$ vs. 84.2 ±10.6 (64–100), p=ns +39% vs. + 14% improvement **12 months:** 93.9 ±6.2 (78–100), $p < 0.001$ vs. 84.0 ±10.6 (65–100), p=ns Significant difference between both groups in favour to AMIC+ ($p < 0.05$, effect size 1.14, mean difference 9.9, 95%-CI 2.1–17.6) **24 months**: 96.1 ±3.8 (88–100), $p < 0.001$ vs. 93.1 ±4.3 (90–100), $p < 0.001$ Significant improvement in both groups **60 months:** 91.4 ±7.2 (76–100), $p < 0.001$ vs. 88.3 ±9.6 (70–100), $p < 0.05$ **100 months:** 89.1 ±6.0 (80–100), $p < 0.001$ vs. 85.6 ±9.4 (73–100), p=ns 60- + 100-month FU slight progressive reduction, AMIC+ always significantly higher than baseline
TAS mean SD (range) *Higher scores indicate improved ADL*	**Pre-injury:** 6.0 ±1.8 (3–9) vs. 6.2 ±1.7 (3–9) **Pre-operative:** 4.3 ±2.5 (1–9) vs. 4.7 ±2.8 (2–9) **6 months:** 3.6 ±0.9 (2–5), p=ns vs. 4.5 ±2.0 (3–9), p=ns **12 months**: 5.0 ±1.8 (3–9), p=ns vs. 5.6 ±1.9 (2–9), p=ns **24 months:** 5.4 ±2.0 (2–9), p=ns vs. 6.3 ±2.2 (3–10), p=ns **60 months:** 5.0 ±2.2 (2–9), p=ns vs. 5.6 ±1.4 (3–7), p=ns **100 months:** 4.7 ±1.3 (3–7), p=ns vs. 4.9 ±2.5 (1–8), p=ns No significant lower scores than the pre-injury level, return to pre-injury levels in both groups starting at 12-month FU, further increase up to 24 months
ICRS mean (SD)	NR
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: physical functioning (PF), physical role (PR), vitality (VI) mean (SD) *Higher scores indicate better function*	NR

[50] International Knee Documentation Committee score:
A=normal; B=nearly normal; C=abnormal, D=severely abnormal.

Author, year	De Girolamo et al. 2019 [94]
Pain	
VAS mean SD (range) *Lower scores indicate less pain*	**Baseline:** 6.6 ±2.7 (1–10) vs. 5.8 ±2.2 (2–8) **6 months:** 1.9 ±1.4 (0–8), p < 0.001 vs. 3.3 ±1.8 (0–7), p < 0.05 -72% significant improvement vs. -42 % significant improvement **12 months:** 1.1 ±1.3 (0–3.5), p < 0.001 vs. 3.0 ±1.8 (0–6), p < 0.01 AMIC+ significant lower than AMIC, p < 0.05, no significant improvement in time **24 months:** 0.6 ±0.8 (0–2), p < 0.001 vs. 0.8 ±0.9 (0–2), p < 0.001 Minimum level of pain in both groups **60 months:** 1.2 ±1.3 (0–4), p < 0.001 vs. 0.9 ±1.4 (0–4), p < 0.001 **100 months:** 0.9 ±1.1 (0–3), p < 0.001 vs. 2.7 ±2.8 (0–8), p < 0.05 Always significantly lower than the pre-operative level (p < 0.05)
KOOS mean (SD)	**KOOS Pain**** **Baseline:** NR*** **60-months:** 65.9 (max. 86.7) vs. 62.6 (max. 79.4) **100-months:** 61.5 (max. 84.2) vs. 62.5 (max. 79.4) Satisfactory in both groups in particular for pain and DA, a slight progressive decrease with time for sport and QOL, no differences between groups
WOMAC Pain subscale mean (%/SD) *Lower scores indicate less pain*	NR
Quality of life	
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: emotional role (ER), psychological well-being (PS) mean (SD) *Higher scores indicate better QoL*	NR
KOOS (QOL)	**KOOS QOL**** **Baseline:** NR*** **60 months**: 57.4 (max. 91.1) vs. 52.3 (max. 87.4) **100 months:** 37.9 (max. 77.1) vs. 18.6 (max. 57.8) Satisfactory in both groups in particular for pain and DA, a slight progressive decrease with time for sport and QOL, no differences between groups
Structural repair	
MR Imaging	**12-/24-months:** 10/10 vs. 7/10 drop-outs improved surface appearance and MRI signal at AMIC+BMAC and similar defect size and filling in the two groups **6 months:** higher proportion of patients in AMIC+BMAC achieved graft integration (comparable at **12 months)** **24 months:** 30% reduction in bone marrow lesion of the whole cohort (6/20)
MOCART Score *Higher scores indicate more complete defect filling*	no total score reported
Necessity of total joint replacement	NR
Safety	
Complications/adverse events, n (%)	**<12 months:** 0 (0*) vs. 1 (8.3*) (arthrosynovitis)
Serious adverse events, n (%)	NR
Procedure-related adverse event, n (%)	NR
Device-related adverse events, n (%)	NR
Re-operation rate, n (%)	0 (0*) vs. 0 (0*)
Procedure related mortality n (%)	NR

Abbreviations: ACI … autologous chondrocyte implantation; ACL … anterior cruciate ligament; ADL … activities of daily living; AE … adverse event; AMIC … autologous matrix-induced chondrogenesis; BMAC … bone marrow aspirate concentrate; BMI … body mass index; CG … control group; CI … confidence interval; DA … daily activities; FU … follow-up; ICRS … International Cartilage Repair Society; IG … intervention group; IKDC … International Knee Documentation

Committee; IQR … interquartile range; KL … Kellgren-Lawrence; KOOS … Knee Injury and Osteoarthritis Outcome Score; m … months; m-BMS … matrix-augmented bone marrow stimulation; MCID … minimal clinically important difference; MD … mean difference; MFx … microfracture; MOCART … magnetic resonance observation of cartilage repair tissue; MRI … magnetic resonance imaging; MSC … mesenchymal stem cells; n.s. … not significant; NCT … national clinical trial; NR … not reported; ns … not significant; OA … osteoarthritis; pts … patients; QoL … quality of life; RCT … randomised controlled trial; s.s. … statistically significant; SD … standard deviation; SE … standard error; SF … Short Form (Health Survey); SSOC … standard of care; TAS … Tegner Activity Scale; VAS … Visual Analogue Scale; vs. … versus; WOMAC … Western Ontario and McMaster Universities Osteoarthritis Index; yrs … years

Note:

** Self-calculated*

*** Counts were not reported. Data was presented in a box plot and was extracted using the WebPlotDigitizer software[103]. It is important to note that data may contain inaccuracies and should be treated with caution. In addition to mean values, only maximum values (max.) are shown in the graph.*

**** For the long-term follow-up, the objective IKDC was replaced by the KOOS, consequently no baseline information for the KOOS reported.*

Table A-5: One-stage matrix assisted cartilage repair with BMAC: Results from observational studies

Author, year	Gobbi et al. 2015 [95]	Gobbi et al. 2016 [96]
Trial register number	**NR**	**Reported but not available.**
Country	Italy	Italy
Sponsor	No funding	One author is a paid consultant for ANIKA Therapeutics
Intervention/Product	One-step scaffold-assisted surgery + BMAC/ ■ 60mL bone marrow (ipsilateral iliac crest) ■ BMAC Centrifugation: commercially available system (BMAC Harvest Smart PreP2 System, Harvest Technologies, Plymouth, MA) ■ microfracturing ■ miniarthrotomy approach ■ Nonseeded 3-dimensional scaffold HYAFF11 (Hyalofast, Anika Therapeutics, Srl, Abano Terme, Italy) anchored with a polydioxanone suture and sealed with fibrin glue	1-stage technique of Hyaluronic Acid–Based Scaffold with BMAC (HA-BMAC)/ ■ 60 mL of bone marrow aspirate (ipsilateral iliac crest) ■ BMAC Centrifugation: commercially available system (BMAC Harvest Smart PreP2 System; Harvest Technologies) ■ Batroxobin enzyme (Plateltex Act; Plateltex SRO) was used to activate the BMAC to produce a sticky clot material. ■ microfracturing ■ miniarthrotomy approach ■ 3-dimensional hyaluronic acid–based scaffold (Hyalofast; Anika Therapeutics Srl) was secured by use of a polydioxanone suture and/or fibrin glue
Comparator	MACI (2-step surgery – cartilage biopsy obtained from knee, biopsy was sent to the laboratory for in vitro isolation and expansion of autologous chondrocytes. Cells were seeded into the HYAFF 11 scaffold (Hyalograft C scaffold, Anika Therapeutics Srl, Abano Terme, Italy) for 2 weeks. At a second stage, implantation was carried out through a mini-arthrotomy	MFx (1-step surgery) alone – Removal of all unstable cartilaginous flaps and layers of calcified cartilage, drilling holes in subchondral plate (3 to 4mm apart) to release bone marrow elements
Study design	Prospective non-randomized controlled trial (NRCT)	Prospective non-randomized controlled trial (NRCT); HA-BMAC group if the health insurance policy of the treating institution supported this option; MF group if HA-BMAC treatment was not available
Study duration	2005-2010	2005-2010
Blinding	non-blinded[51]	non-blinded
Number of pts	37 (18 vs. 19)	Surgery: 52* (27 vs. 25) Final analysis: 50 (25 vs. 25)
Female, n (%)	8 (44.44)* vs. 10 (52.63*), p=0.6184	9 (36)* vs. 9 (36*), p>0.999
Inclusion criteria	■ aged 30-60 yrs ■ BMI 20-30 kg/m^2 ■ patients with grade 4 cartilage lesions as per the ICRS classification of patella or trochlea; with size ≥4 cm^2; treated by a mini-arthrotomy approach with the same hyaluronan scaffold ■ clinical symptoms of pain, swelling, locking or giving way	■ aged 30-60 yrs ■ BMI 20-30 kg/m^2 ■ diagnosis of grade IV cartilage lesion (ICRS classification) of at least 1 cm^2 affecting a femoral condyle or the patellofemoral articulation ■ participation in a sporting event at least twice per week ■ availability of 2- and 5-year follow-up assessments
Exclusion criteria	■ uncorrected malalignment, ligament insufficiency or patellofemoral maltracking, deep osteochondral lesions requiring bone grafting, tricompartmental arthritis, osteonecrosis	■ tricompartmental arthritis or osteonecrosis of the knee ■ multiple prior corticosteroid injections ■ general systemic illness, neurovascular disease

[51] Outcome assessors were blinded.

Author, year	Gobbi et al. 2015 [95]	Gobbi et al. 2016 [96]
Exclusion criteria *(continuation)*	■ patients with other general medical conditions (diabetes, rheumatoid arthritis, etc) ■ multiple, recent (<3 months) intra-articular injections with steroids ■ deformity or osteoarthritis at ipsilateral and contralateral hip, knee, or ankle joints ■ noncompliance to follow the rehabilitation protocol	■ inability to follow the rehabilitation protocol
Primary endpoint(s)	VAS, IKDC objective/subjective, KOOS subscales, TAS, Radiographs, + MRI at 24 months and final (min. 36 months) follow-up	IKDC objective/subjective, TAS + Lysholm score at 24- and 60-months follow-up
Secondary endpoint(s)	NR	IKDC, KOOS, TAS, Lysholm categorised by age, lesion size, and lesion count at 60 months follow-up
Prior surgery, n (%)	NR	NR
Age of patients, mean, yrs ±SD	45.5 ±7.55 vs. 43.10 ±5.81, p=0.286	47.0 ±7.0 vs. 42.9 ±7.7, p=0.035[52]
Postoperative treatment(s)	4-phase rehabilitation protocol (no details reported)	Staged rehabilitation protocol Supervised by a physical therapist ■ week 0-4: Weightbearing restricted, beginning of touchdown weightbearing (week 3-4); ■ week 0-6: focusing on controlling pain, reducing effusion, maintaining range of motion, and minimizing muscle atrophy ■ Pool-based therapy ■ week 9: initiated active functional training ■ weeks 11-32: progression to running was aided by the use of proprioceptive exercises as well as strength, endurance, and aerobic training.
Follow-up (months)	minimum 36 months Average 54.16 months (range 38-77.8) vs. 59.69 months (range 48.2-74.7)	60
Loss to follow-up, n (%)	0 (0) vs. 0 (0)	2 (2 vs. 0)
BMI, mean, kg/m², ±SD	24.77 ±2.75 vs. 24.31 ±1.37 (p=0.520)	NR
Defect size, mean, cm² (SD)	Total lesion area (cm²)/patient 10.48 ±6.01 vs. 9.73 ±6.09, p=0.673 Average lesion size (cm²)/lesion 5.45 vs. 7.12, p=0.174	**median (interquartile range[53]), cm²** 6.5 (6.3) vs. 4.5 (1.5), **p=.003**[52]
Location of lesion, n (%)	Patellofemoral, 18 (100) vs. 19 (100)	Medial femoral condyle, 15 (NR) vs. 15 (NR)[54], p=0.016[52] Lateral femoral condyle, 1 (NR) vs. 11 (NR) Patella, 8 (NR) vs. 3 (NR) Other, 8 (NR) vs. 11(NR)
Clinical classification, n (%)	Aetiology (p=0.5560): traumatic, 13 (72.2*) vs. 12 (63.2*); degenerative, 5 (27.8*) vs. 7 (36.8*) Lesion size, cm² (p=0.9092): ≤10, 12 (66.7*) vs. 13 (68.4*); >10, 6 (33.3*) vs. 6 (31.6*) Lesion number (p=0.2536): single, 8 (44.4*) vs. 12 (63.2*); multiple, 10 (55.6*) vs. 7 (36.8*)	Aetiology (p=0.069): traumatic, 20 (80.0*) vs. 14 (56.0*); nontraumatic, 5 (20.0*) vs. 11 (44.0) Lesion size, cm², (p < 0.999): ≤4, 8 (32.0*) vs. 8 (32.0*); > 4, 17 (68.0*) vs. 17 (68.0*) Lesion number (p=0.087): single, 17 (68.0*) vs 11 (44.0*); multiple, 8 (32.0*) vs. 14 (56.0*)
BMAC concentration factor	4- to 6-fold	Approximately 6-fold

[52] Statistically significant difference between groups (p<.05).

[53] Interquartile range = third quartile – first quartile.

[54] Values in this category are not reported per patient, but are aggregated from single and multiple lesions, so percentages have not been calculated for consistency.

Author, year	Gobbi et al. 2015 [95]	Gobbi et al. 2016 [96]
Outcomes		
Efficacy		
Physical function, activity (e.g. KOOS, Lysholm score, TAS, IKDC), mean (± SD)		
KOOS mean (SD)	**KOOS Symptoms** **Baseline:** 56.39 (±14.86) vs. 50.53 (±13.22) **24 months:** 84.94 (±11.92) vs. 86.05 (±9.47) **Final FU (min. 36 months):** 90.61 (±10.85) vs. 81.05 (±11.04), p=0.430 **KOOS ADLs** **Baseline:** 64.17 (±17.35) vs. 50.42 (±12.50) **24 months:** 88.67 (±10.90) vs. 85.94 (±13.66) **Final FU:** 90.61 (±10.85) vs. 81.05 (±11.04), p=0.430 **KOOS Sport/rec** **Baseline:** 33.33 (±22.09) vs. 32.21 (±16.92) **24 months:** 68.78 (±23.36) vs. 71.42 (±14.16) **Final FU:** 79.72 (±17.37) vs. 68.84 (±15.25), p=0.173 Significant improvement in all the evaluated scores at 2-year and final follow-up (all pts), compared to preoperative scores (p=0.001) Significant benefit of BMAC throughout the entire postoperative period of KOOS symptoms (p=0.001) and Sport/rec (p=0.003).	**median (IQR)** **KOOS Symptoms**[++] **Baseline:** NR **24 months:** NR **60 months:** 90 (12) vs. 87 (23), p=0.060 **KOOS ADLs**[++] **Baseline:** NR **24 months:** NR **60 months:** 95 (20) vs. 95 (23), p=0.217 **KOOS Sport/rec**[++] **Baseline:** NR **24 months:** NR **60 months:** 85 (17) vs. 68 (37), **p=0.013+**
IKDC mean (SD) *Higher scores indicate better function*	**IKDC Objective** **Baseline:** 8C, 10D vs. 9C, 10D **24 months:** 12A, 6B vs. 15A, 4B **Final FU (min. 36 months):** 14A, 4B vs. 10A, 8B, 1C, p=0.12 **IKDC Subjective** **Baseline:** 38.78 (±19.18) vs. 46.37 (±14.44) **24 months:** 74.67 (±13.90) vs. 81.05 (±8.31) **Final FU:** 82.52 (±10.72) vs. 75.70 (±9.85), p=0.015 significant improvement in all the evaluated scores at 2-year and final follow-up (all pts), compared to preoperative scores (p=0.001). Statistically significant benefit of BMAC + MACI in entire postoperative period for IKDC subjective (p < 0.001).	**IKDC Objective** (A/B/C/D), No. **Baseline:** 0/1/12/12 vs. 0/2/8/15, p=0.552 **24 months:** 16/9/0/0 vs. 4/12/9/0, **p<0.001+** **60 months:** 19/6/0/0 vs. 2/5/13/5, **p<0.001+** **IKDC Subjective median (IQR)** **Baseline:** 40 (29) vs. 42 (24), p=0.143 **24 months:** 83 (15) vs. 80 (25), p<0.763 **60 months:** 86 (14) vs. 77 (26), p=0.086 IKDC objective + IKDC subjective scores significantly improved in IG at 2-year follow-up (p< 0.001) Improvement in IKDC objective in IG at 5-year follow-up (p=0.063) A significantly greater proportion of patients in IG, compared with CG, were classified as normal or nearly normal at 2- and 5-year follow-up according to the IKDC objective scores.
WOMAC mean (%/SD) *Lower scores indicate better function*	NR	NR
Modified Cincinnati Knee total score *Higher scores indicate better function*	NR	NR

Author, year	Gobbi et al. 2015 [95]	Gobbi et al. 2016 [96]
Lysholm Score mean (SD)	NR	**median (IQR)** **Baseline**: 45 (10) vs. 45 (25), p=0.815 **24 months:** 90 (25) vs. 90 (12), p=0.845 **60 months:** 90 (17) vs. 80 (20), p=0.178 IG significantly improved at 2-year follow-up (p< 0.001)
TAS mean (SD) *Higher scores indicate improved ADL*	**Baseline:** 2.33 (±1.18) vs. 2.1 (±0.73) **24 months:** 5.61 (±1.41) vs. 5.57 (±0.83) **Final FU (min. 36 months):** 6.05 (±1.10) vs. 5.26 (±1.14), p=0.220 significant improvement in all the evaluated scores at 2-year and final follow-up (all pts), compared to preoperative scores (p=0.001).	**median (IQR)** **Baseline**: 2 (2) vs. 3 (1), p=0.077 **24 months:** 5 (1) vs. 5 (2), p=0.115 **60 months:** 6 (1.5) vs. 4 (2), **p<0.001+** IG significantly improved at 2-year follow-up (p< 0.001)
ICRS mean (SD)	NR	NR
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: physical functioning (PF), physical role (PR), vitality (VI) mean (SD) *Higher scores indicate better function*	NR	NR
Pain		
VAS mean (SD) *Lower scores indicate less pain*	**Baseline:** 5.33 (±1.32) vs. 5.53 (±0.90) **24 months:** 0.72 (±1.01) vs. 0.47 (±0.61) **Final FU (min. 36 months):** 0.33 (±0.68) vs. 0.84 (±0.68), p=0.418 Significant reduction (p=0.001) significant benefit of BMAC throughout the entire postoperative period (p=0.004).	NR
KOOS (PAIN) mean (SD)	**Baseline**: 56.44 (±14.13) vs. 44.26 (±14.46) **24 months:** 90.33 (±10.15) vs. 83.26 (±10.59) **Final FU (min. 36 months):** 93.50 (±8.22) vs. 80.73 (±11.79), p=0.336 significant improvement in all the evaluated scores at 2-year and final follow-up (all pts), compared to preoperative scores (p=0.001). Difference in improvement between the 2 groups was nonsignificant (p>0.05).	**median (IQR)**$^{++}$ **Baseline**: NR **24 months:** NR **60 months:** 95 (10) vs. 87 (31), **p=0.023+**
WOMAC **Pain subscale** Mean (%/SD) *Lower scores indicate less pain*	NR	NR
Quality of life		
Short Form Health Survey (SF-36, SF-12, SF-8) Subscale: emotional role (ER), psychological well-being (PS) mean (SD) *Higher scores indicate better QoL*	NR	NR

Author, year	Gobbi et al. 2015 [95]	Gobbi et al. 2016 [96]
KOOS (QOL) mean (SD)	**Baseline**: 32.83 (±18.31) vs. 33.63 (±10.74) **24 months:** 76.00 (±18.52) vs. 79.26 (±15.09) **Final FU (min. 36 months):** 84.00 (±14.81) vs. 76.10 (±16.90), p=0.107 significant improvement in all the evaluated scores at 2-year and final follow-up (all pts), compared to preoperative scores (p=0.001).	**median (IQR)** ++ **Baseline**: NR **24 months:** NR **60 months:** 85 (20) vs. 80 (39), p=0.289
Structural repair		
MR Imaging n (%)	**Final FU (min. 36 months):** Complete or near complete (>50%): NR (81%) vs. NR (76%) No signs of hypertrophy in either group. Complete Integration with adjacent cartilage: NR (93.7%) vs. NR (88.2%) Subchondral oedema: 2 (NR) vs. 2 (NR) No cysts or sclerosis of subchondral bone in either of the groups	NR
MOCART Score *Higher scores indicate more complete defect filling*	NR	NR
Necessity of total joint replacement	NR	NR
Safety		
Complications/adverse events, n (%)	No adverse reactions or postoperative infections were noted	No complications resulted from the procedure to harvest BMAC Stiffness requiring manipulation under anaesthesia 1 vs. 0
Serious adverse events, n (%)	NR	No serious adverse events
Procedure-related adverse event, n (%)	NR	NR
Device-related adverse events, n (%)	NR	NR
Re-operation rate, n (%)	Debridement and mobilisation (intraarticular adhesions) at 7 and 6 months postoperatively: 1 vs. 1	0 (0) vs. 4 (14.1*)
Procedure related mortality n (%)	NR	NR

Abbreviations: ADL … activities of daily living; AMIC … autologous matrix-induced chondrogenesis; BMAC … bone marrow aspirate concentrate; BMI … body mass index; CG … control group; FU … follow-up; HA … hyaluronic acid; ICRS … International Cartilage Repair Society; IG … intervention group; IKDC … International Knee Documentation Committee; IQR … interquartile range; KOOS … Knee Injury and Osteoarthritis Outcome Score; MACI … matrix-induced autologous chondrocyte implantation; MFx … microfracture; MRI … magnetic resonance imaging; n … number; NR … not reported; NRCT … non-randomized controlled trial; ns … not significant; pts … patients; QoL … quality of life; SD … standard deviation; TAS … Tegner Activity Scale; VAS … Visual Analogue Scale; vs. … versus; WOMAC … Western Ontario and McMaster Universities Osteoarthritis Index; yrs … years

Note:

** Self-calculated*

+ Statistically significant difference between groups (p<.05).

++ The KOOS Score was only available after 5 yrs follow-up because of the recent validation of this tool for the Italian language.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in HTA-R and EUnetHTA guidelines [65].

Table A-6: Risk of bias – study level (randomised studies) see [69]

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Altschuler 2024 [45]	PROM	Low	Some concerns[a]	Low	Some concerns[b]	Low	Some concerns
	CROM	Low	Some concerns[a]	Low	Low	Low	Some concerns
Anders [44] + Volz 2017 [88] (FU Volz 2024 [89])	PROM	Low (Low)	Some concerns[c] (Some concerns)	Some concerns[d] (Some concerns)	Some concerns[b] (Some concerns)	Some concerns[j] (Some concerns)	High (High)
	CROM	Low (Low)	Some concerns[c] (Some concerns)	Some concerns[d] (Some concerns)	Low (Low)	Some concerns (Some concerns)	High (High)
Fossum [49]	PROM	Some concerns[e]	Some concerns[c]	Low	Some concerns[f]	Low	High
	CROM	Some concerns	Some concerns	Low	Some concerns	Low	High
Glasbrenner [90]	PROM	Some concerns[e]	Some concerns[c]	Low	Low	Low	Some concerns
	CROM	Some concerns[e]	Some concerns[c]	Low	Low	Low	Some concerns
Kim [91]	PROM	Low	High[f]	Some concerns[g]	Some concerns[b]	Low	High
	CROM	Low	High	Some concerns[g]	Some concerns	Low	High
Kon [43]	PROM	Low	Some concerns[c]	Some concerns[g]	Some concerns[b]	Low	High
	CROM	Low	Some concerns[c]	Some concerns[g]	Low	Low	Some concerns
Stanish [92] (FU Shive [93])	PROM	Low (Low)	Some concern[c] (Some concern)	Low (High[g])	Some concerns (Some concerns	Low (Low)	Some concerns (High)
	CROM	Low (Low)	Some concern[c] (Some concern)	Low (High)	Low (Low)	Low (Low)	Some concern (High)
De Girolamo [94]	PROM	Low	High[h]	High[i]	Some concern[c]	Low	High
	CROM	Low	High[h]	High[i]	Some concern[c]	Low	High

Abbreviations: CROM … clinician-reported outcome measure; FU … follow-up, PROM … patient-reported outcome measure

Comments:

[a] *no blinding, no ITT was conducted*
[b] *assessors were aware of the intervention*
[c] *no blinding*
[d] *data not available for nearly all patients and no sensitivity analysis was conducted*
[e] *significant differences in multiple baseline characteristics*
[f] *no blinding, not ITT and no sensitivity analysis were conducted*
[g] *high dropout rate*
[h] *no blinding, no protocol available, no ITT was conducted*
[i] *high dropout rate, no sensitivity analysis was conducted*
[j] *no preregistered protocol*

Table A-7: Risk of bias – study level (non-randomised studies), see [70]

Trial	Endpoints	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Gobbi 2015 [95]	PROM	Moderate[a]	Low	Low	Moderate[b]	Low	Moderate[c]	Low	Moderate	
	CROM	Moderate[a]	Low	Low	Moderate[b]	Low	Low	Low	Moderate	
Gobbi et al. (2016) [96]	PROM	Serious[d]	Moderate[e]	Low	NI	Critical[e]	Serious[f]	Low	Critical	
	CROM	Serious[d]	Moderate[e]	Low	NI	Critical[e]	Serious[f]	Low	Critical	

Abbreviations: NI … no information.

Comments:

[a] *no randomisation*

[b] *not enough information to derive conclusions*

[c] *patients were aware of the intervention*

[d] *no adjustment for confounders*

[e] *lost to follow up excluded*

[f] *non blinded assessment*

Table A-8: Evidence profile: efficacy and safety of AMIC versus MFx in patients with cartilage defects

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised I	N of pts randomised C	Effect	Certainty
Physical function/activity level/symptoms: improvement from baseline (FU at ≤24 months: assessed with IKDC, 0-100, higher scores indicate better function)										
4	RCT	serious[a]	very serious[c]	not serious	serious[e]	none	295	210	**AMIC vs. MFx** Total MD=7.06 [95%CI: -3.9;18.0]	⊕⊕◯◯ low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months assessed with KOOS total, 0-100, higher scores indicate better function)										
2	RCT	serious[a]	serious[d]	not serious	not serious	none	219	132	**AMIC vs. MFx:** Altschuler MD 22.5 (95%CI 17.0;28.0), **p<0.0001** Kim MD 1.9 (95%CI -3.9;7.7)	⊕⊕◯◯ low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months assessed with WOMAC physical function, 0-96, lower scores indicate better function)										
1	RCT	serious[a]	NA	not serious	serious[e]	none	41	39	AMIC vs. MFx Shive: **Change after 12 months** MD=4.7 [95%CI: -7.22;16.62], NS	⊕⊕◯◯ low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with WOMAC physical function, 0-96, lower scores indicate better function)										
1	RCT	very serious[b]	NA	not serious	serious[e]	none	41	39	AMIC vs. MFx Shive: **Change after 60 months:** MD=5.6 [95%CI: -5.7;16.8], NS	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU at 24 months: assessed with Modified Cincinnata Scale, 0-100, higher scores indicate better function)										
1	RCT	serious[a]	NA	not serious	serious[f]	none	34	13	**AMIC vs. MFx** Anders/Volz: (means ±SD)[55],: at 24 months: 85 (±18) | NR vs. 74 (±26); Change after 24 months: NR | +37* vs. +36*	⊕⊕◯◯ low
Physical function/activity level/symptoms: improvement from baseline (FU > 24 months: assessed with Modified Cincinnata Scale, 0-100, higher scores indicate better function)										
1	RCT	very serious[b]	NA	not serious	serious[e]	none	34	13	**AMIC vs. MFx** Anders/Volz: at 60 months: significant changes within all groups (p<0.01) At 120 months: MD=26.9 [95%CI: 14.8;38.9]	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed wiith SF-36, 0-100, higher scores indicate better function)										
1	RCT	serious[a]	NA	not serious	serious[e]	none	41	39	**AMIC vs. MFx** Shive: **Change after 12 months:** MD=-1.8 [95%CI -5.9;2.3]	⊕⊕◯◯ low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed wiith SF-36, 0-100, higher scores indicate better function)										
1	RCT	serious[a]	NA	not serious	serious[e]	none	41	39	**AMIC vs. MFx** Shive: **Change after 60 months**: MD=-1.4 [95%CI -5.7;2.8]	⊕⊕◯◯ low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with TAS, 0-10, higher scores indicate better function)										
1	RCT	serious[b]	NA	not serious	serious[e]	none	61	63	**AMIC vs. MFx** Kon (mean (range)): 4.0 (1.0-9.0) vs. 4.0 (2.0-8.0)[56] **Change after 24 months:** +1.0* vs. +1.0*	⊕⊕◯◯ low

[55] IG glued | IG sutured vs. CG.

[56] Sample size assumed > OIS (21 per group).

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised		Effect	Certainty
							I	C		
Quality of life: Improvement from baseline (FU at ≤24 months, assessed with SF-36, 0-100, higher scores indicate better function)										
1	RCT	serious[a]	NA	not serious	not serious	none	41	39	**AMIC vs. MFx** Shive: Change after 12 months: MD=2.7 [95%CI: -1.9;7.3]	⨁⨁◯◯ low
Quality of life: Improvement from baseline (FU at >24 months, assessed with SF-36, 0-100, higher scores indicate better function))										
1	RCT	very serious[b]	NA	not serious	not serious	none	41	39	**AMIC vs. MFx** Shive: Change after 60 months: MD=2.9 [95%CI: -1.5;7.2]	⨁◯◯◯ very low
Quality of life: Improvement from baseline (FU at ≤24 months assessed with KOOS QoL; 0-100, higher scores indicate higher QoL)										
3	RCT	serious[a]	not serious	not serious	serious[e]	none	243	162	**AMIC vs. MFx** Altschuler (mean): 73.9 vs. 48.8 Glasbrenner (median (IQR, 95%CI)): 62.4 (48.6-71.9; 24.5-99.8) vs. 68.8 (49.9-81.1; 24.5-99.8, p: NR Kon (mean): 54.1 vs. 55.3; mean change*: 26.3 vs. 31.5	⨁⨁◯◯ low
Pain: reduction from baseline (FU ≤24 months, assessed with VAS, 0-100, lower scores indicate less pain)										
3	RCT	serious[a]	not serious	not serious	serious[e]	none	128	126	**AMIC vs. MFx Total MD=-2.27 [95%CI: -7.42; 2.9]**	⨁⨁◯◯ low
Pain: reduction from baseline (FU >24 months, assessed with VAS, 0-100, lower scores indicate less pain)										
1	RCT	very serious[b]	not serious	not serious	serious[e]	none	34	13	**AMIC vs. MFx** Volz: At 60 months: 11 (±20) | 15 (±22) vs 30 (±19) At 120 months: 12 (±21) | 11 (±16) vs 31 (±20), NS	⨁◯◯◯ very low
Pain: reduction from baseline (FU at ≤24 months , assessed with KOOS pain, 0-100, higher scores indicate less pain)										
4	RCT	serious[a]	not serious	not serious	serious[e]	none	295	210	**AMIC vs. MFx** Altschuler (mean) 89.5 vs. 69.1 Glasbrenner (median (IQR, 95%CI) 90.3 (82.5-95.2; 63.7-97.5) vs. 91.8 (83.3-99.9; 69.6-99.9) Kim MD=4.4 [95%CI: -1.2;9.9] Kon (mean):77.6 vs. 79.4; mean change*: 18.2 vs. 21.9	⨁⨁◯◯ low
Pain: reduction from baseline (FU ≤24 months assessed with WOMAC pain, 0-96, lower scores indicate less pain)										
1	RCT	serious[b]	not serious	not serious	serious[e]	none	41	39	**AMIC vs. MFx** Shive: Change after 12 months: MD=0.7 [95%CI: -2.6;4.0]	⨁⨁◯◯ low
Pain: reduction from baseline (FU >24 months, assessed with WOMAC pain, 0-96, lower scores indicate less pain)										
1	RCT	very serious[b]	not serious	not serious	serious[e]	none	41	39	**AMIC vs. MFx** Shive: Change after 60 months: MD=1.2 [95%CI: -2.5; 4.9]	⨁◯◯◯ very low

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised		Effect	Certainty
							I	C		
Structural repair: defect filling (≤24 months assessed with %)										
6	RCT	serious[a]	not serious	not serious	not serious	none	370	262	**AMIC vs. MFx** Altschuler: ≥75% defect fill: 88.5% vs. 30.9% (p<.0001), <50% defect fill: 1.3% vs. 50% Volz: >66.7% defect filling: 60.0% vs. 25.0% Glasbrenner: >50% of defect filling in both groups Kim (n pts (%) <50%: 5 (6.1) vs. 14 (17.1), **p=0.0377**, ≥50%: 37 (45.1) vs. 26 (31.7), p=NR Kon (mean %) 49.0 vs. 65.9, p=NS Shive (mean ±SD): At 12 months: 92.8 (±2.0) vs. 85.2 (±2.1), **p=0.011**	⨁⨁⨁◯ moderate
Structural repair: defect filling (>24 months assessed with %)										
1	RCT	very serious[a]	NA	not serious	serious[e]	none	41	39	**AMIC vs. MFx** Shive (mean ±SD): At 60 months: 93.79 (±1.16) vs. 86.96 (±2.85), p=0.017	⨁◯◯◯ very low
Structural repair: (FU ≤24 months assessed with MOCART total score, 0-100, higher scores indicate better repair)										
1	RCT	serious[a]	NA	not serious	serious[e]	none	52	48	**AMIC vs. MFx** Kim (24 months): MD=5.2 [95%CI: -2.6;12.9]	⨁⨁◯◯ low
Structural repair: (FU >24 months assessed with MOCART total score, 0-100, higher scores inidcate better repair)										
1	RCT	very serious[a]	NA	not serious	serious[e]	none	34	13	**AMIC vs. MFx** Volz (120 months) MD=-5 [95%CI: -25.7;15.7]	⨁◯◯◯ very low
Necessity of total joint replacement (FU >24 months assessed with: in % pts)										
1	RCT	very serious[a]	NA	not serious	serious[r]	none	34	13	**AMIC vs. MFx** Volz: At 60 months: 1 (5.9*) | 0 (0.0) vs. 0 (0.0)	⨁◯◯◯ very low
Safety: adverse events (≤24 months) assessed with in % of pts)										
5	RCT	serious[a]	not serious	not serious	serious[f]	none	318	214	**AMIC vs. MFx 24 months:** Altschuler: ≥1 AE in 98 (58.7) vs. 65 (77.4) patients Volz: 13 adverse events in 9 pts. Glasbrenner: 3 (25.0*) vs. 3 (25.0*) Kon: 13 (21.0*) vs. 4 (6.5*) Shive: **12 months** (41 vs. 37 pts.): 40 (98.0) vs. 36 (92.0) n.s.	⨁⨁◯◯ low
Safety: adverse events (>24 months) assessed with in % of pts)										
1	RCT	very serious[a]	NA	not serious	serious[f]	none	41	39	AMIC vs. MFx Shive **60 months** (34 vs. 26 pts.): 13 (19.0) vs. 18 (27.0); p=NR	⨁◯◯◯ very low

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised		Effect	Certainty
							I	C		
Safety: severe adverse events (FU ≤24 assessed with: in % of pts)										
6	RCT	serious[a]	not serious	not serious	serious[f]	none	370	262	**AMIC vs. MFx 24 months** Altschuler: ≥1 serious AE: 26 (15.6) vs. 17 (20.2) Volz: 0 (0.0) vs. 0 (0.0) Glasbrenner: 1 (8.3*) vs. 1 (8.3*) Kim: 2 (4.4*) vs. 2 (4.6*) Kon: 3 (4.8*) vs. 1 (1.6*) **12 months** Shive (41 vs. 37 pts): 5 (12.2*)[41] vs. 1 (2.7*)	⨁⨁◯◯ low
Safety: severe adverse events (FU >24 assessed with: in % of pts)										
1	RCT	very serious[b]	NA	not serious	serious[f]	none	41	39	**AMIC vs. MFx** Shive: **60 months** (34 vs. 26 pts.): 0 (0) vs. 1 (3.8*)	⨁◯◯◯ very low

Abbreviations: AE … adverse event; AMIC … autologous matrix-induced chondrogenesis; CI … confidence interval; FU … follow-up; IKDC … International Knee Documentation Committee; IQR … interquartile range; KOOS … Knee Injury and Osteoarthritis Outcome Score; MD … mean difference; MFx … microfracture; MOCART … magnetic resonance observation of cartilage repair tissue; N … number; NR … not reported; NS … not significant; pts … patients; QoL … quality of life; RCT … randomized controlled trial; SD … standard deviation; SF-36 … Short Form-36; VAS … Visual Analog Scale; vs. … versus; WOMAC … Western Ontario and McMaster Universities Osteoarthritis Index.

Note: If serious or very serious, please give reasons for the classification (mandatory)

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Comments:

[a] *Downgraded due to non-blinding or high drop-out rates*

[b] *Downgraded due to high drop-out rates (long-term follow-up)*

[c] *High heterogeneity (I^2>90%)*

[d] *High heterogeneity (e.g. non-overlapping confidence intervals*

[e] *Imprecision due to wide confidence intervals*

[f] *Imprecision due to low number of patients and/or no power calculations*

Table A-9: Evidence profile: efficacy and safety of AMIC versus ACI in patients with cartilage defects

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised		Effect	Certainty
							I	C		
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months assessed with KOOS total, 0-100, higher scores indicate better function)										
1	RCT	very serious[a]	NA	not serious	not serious	none	20	20	**AMIC vs. ACI:** Fossum (mean delta between groups): 18.1 vs. 10.3, p=0.17	⨁◯◯◯ very low
physical function/activity level/symptoms: improvement from baseline (fu ≤24 months: assessed with lysolm score, 0-100, higher socres indicate better function)										
1	RCT	very serious[a]	NA	not serious	serious	none	20	21	**AMIC vs. ACI** Fossum (mean (95% CI)): 70.1 (61.0-79.6) vs. 69.6 (62.2 76.9); mean delta between groups: 19.7 vs. 17.0, p=0.66	⨁◯◯◯ very low
Quality of life: Improvement from baseline (FU at ≤24 months, assessed with SF-36, 0-100, higher scores indicate better function)										
NR										
Pain: reducation from baseline (FU ≤24 months, assessed with VAS, 0-100, lower scores indicate less pain)										
1	RCT	very serious[a]	NA	not serious	serious	none	20	21	**AMIC vs. ACI** Fossum (mean (95%CI)): 27.0 (17.1-37.0) vs. 30.4 (20.1-41.2); MD at 24 months: 30.6 vs. 19.6, p=0.19	⨁◯◯◯ very low
Pain: reduction from baseline (FU at 24 months , assessed with KOOS pain, 0-100, higher scores indicate less pain)										
1	RCT	very serious[a]	NA	not serious	very serious[f]	none	20	21	**AMIC vs. ACI** Fossum: Values NR (Subscales: at 24 months the mean difference was higher in the AMIC group, but the difference was not statistically significant)	⨁◯◯◯ very low
Structural repair: defect filling (≤24 months assessed with %)										
NR										
Structural repair: (FU ≤24 months assessed with MOCART total score, 0-100, higher scores indicate better repair)										
NR										
Necessity of total joint replacement (FU >24 months assessed with: in % pts)										
NR										
Safety: adverse events (≤24 months) assessed with in % of pts)										
NR										
Safety: severe adverse events (FU ≤24 assessed with: in % of pts)										
6 + 1	RCT	Very serious[a]	Not serious	Not serious	serious[h]	none	20	21	**AMIC vs. ACI** Fossum: 0 (0.0) vs. 0 (0.0)	⨁◯◯◯ very low

Abbreviations: ACI … autologous chondrocyte implantation; AMIC … autologous matrix-induced chondrogenesis; CI … confidence interval; FU … follow-up; KOOS … Knee Injury and Osteoarthritis Outcome Score; MD … mean difference; MOCART … magnetic resonance observation of cartilage repair tissue; NA … not applicable; NR … not reported; pts … patients; RCT … randomized controlled trial; SF-36 … Short Form-36; VAS … Visual Analog Scale; vs. … versus.

Note: If serious or very serious, please give reasons for the classification (mandatory)

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Comments:

[a] *High risk of bias in at least one domain/some concerns in multiple domains (mainly due to non-blinding, high drop-out rates, no sensitivity analysis*

[b] *Some concerns in risk of bias (some concerns in one or two domains, mainly due to non-blinding)*

[c] *High heterogeneity (I^2>90%)*

[d] *High heterogeneity (e.g. non-overlapping confidence intervals*

[e] *Imprecision due to wide confidence intervals (10-15 points)*

[f] *Imprecision due to wide confidence intervals (>15 points)*

[g] *Imprecision due to low number of patients and no power calculations*

[h] *Imprecision due to low number of patients and events*

Table A-10: Evidence profile AMIC+ versus AMIC in patients with cartilage defects

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised I	N of pts randomised C	Effect	Certainty
Physical function/activity level/symptoms: improvement from baseline (FU mean ≤24 months: assessed with IKDC; A=normal, B=nearly normal, C=abnormal, D=severely abnormal)										
1	randomised trial	very serious[a]	NA	not serious	serious[d]	none	12	12	**Objective (A/B/C/D, No.)** A was significantly increased compared to pre-op ($p < 0.05$); higher percentage of pts. in A compared to B/C/D ($p<0.5$) vs. no significant difference	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU at >24 months: assessed with KOOS; 0-100, higher scores indicate fewer symptoms/better function)										
1	randomised trial	very serious[a]	NA	not serious	very serious[l]	none	12	12	**60 months** **Symptoms:** 76.1 (max. 86.0) vs. 67.0 (max. 90.4)[c] **ADLs:** 83,8 (max. 88,2) vs. 82.7 (max. 87.4)[c] **Sport/rec:** 62.2 (max. 84.9) vs. 49.4 (max. 83.8)[c] **100 months** **Symptoms:** 67.1 (max. 86.0) vs. 67.0 (max. 90.4)[c] **ADLs:** 78.7 (max. 89.6) vs. 74.0 (max. 87.9)[c] **Sport/rec:** 29.7 (max. 84.8) vs. 41.9 (max. 87.2)[c]	⊕◯◯◯ very low

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised		Effect	Certainty
							I	C		
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with TAS Score; 0-10, higher score indicates higher activity level)										
1	randomised trial	very serious[a]	NA	not serious	very serious[f, j, m]	none	12	12	MD=-0.9 [95% CI: -2.6;0.8][b], not significant	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with TAS; 0-10, higher score indicates higher activity level)										
1	randomised trial	very serious[a]	NA	not serious	very serious[f, j, m]	none	12	12	**60 months:** MD=-0.6 [95% CI: -2.1;0.9][b], not significant **100 months:** MD=-0.2 [95% CI: -1.9;1.5][b], not significant	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with Lysholm Score; 0-100, higher score indicates better knee function + fewer symptoms)										
1	randomised trial	very serious[a]	NA	not serious	serious[f, m, h, i]	none	12	12	**12 months:** $p < 0.05$, effect size 1.14, mean difference 9.9, 95% confidence interval 2.1–17.6, significant in favour of IG **24 months**: MD=3.0 [95% CI: -0.2;6.2][b], not significant	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with Lysholm Score; 0-100, higher score indicates better knee function + fewer symptoms)										
1	randomised trial	very serious[a]	NA	not serious	serious[f, m, h, i]	none	12	12	**60 months:** MD=3.1 [95% CI: -3.7;9.9][b], not significant **100 months:** MD=3.5 [95% CI: -2.8;9.8][b], not significant	⊕◯◯◯ very low
Quality of life: Improvement from baseline (FU >24 months, assessed with KOOS QoL; 0-100, higher scores indicate better QoL)										
1	randomised trial	very serious[a]	NA	not serious	very serious[n]	none	12	12	**60 months:** 57.4 (max. 91.1) vs. 52.3 (max. 87.4)[c] **100 months:** 37.9 (max. 77.1) vs. 18.6 (max. 57.8)[c]	⊕◯◯◯ very low
Pain: reduction from baseline (FU ≤24 months, assessed with VAS; 0-10, lower scores indicate less pain)										
1	randomised trial	very serious[a]	NA	not serious	serious[o, g]	none	12	12	MD=-0.2 [95% CI: -0.9;0.5][b], not significant	⊕◯◯◯ very low
Pain: reduction from baseline (FU >24 months, assessed with VAS; 0-10, lower scores indicate less pain)										
1	randomised trial	very serious[a]	NA	not serious	very serious[o, f, k]	none	12	12	**60 months:** MD=0.3 [95% CI: -0.8;1.4][b] , not significant **100 months:** MD=-1.8 [95% CI: -3.7;0.1][b] , not significant	⊕◯◯◯ very low
Pain: reduction from baseline (FU >24 months, assessed with KOOS pain; 0-100, higher scores indicate less pain)										
1	randomised trial	very serious[a]	NA	not serious	serious[p]	none	12	12	**60 months:** 65.9 (max. 86.7) vs. 62.6 (max. 79.4)[c] **100 months:** 61.5 (max. 84.2) vs. 62.5 (max. 79.4)[c]	⊕◯◯◯ very low
Structural repair: defect filling (FU **≤24 months,** assessed with %)										
1	randomised trial	very serious[a]	NA	not serious	serious[d, e]	none	12	12	similar defect size and filling in the two groups	⊕◯◯◯ very low
Safety: adverse events (FU **≤24** months, assessed with % of pts)										
1	randomised trial	very serious[a]	NA	not serious	serious[p, e]	none	12	12	0 (0*) vs. 1 (8.3*)	⊕◯◯◯ very low

Abbreviations: ADL … activities of daily living; CI … confidence interval; FU … follow-up; IKDC … International Knee Documentation Committee; KOOS … Knee Injury and Osteoarthritis Outcome Score; MD … mean difference; NA … not applicable; No. … number; pts … patients; QoL … quality of life; rec … recreation; VAS … Visual Analog Scale; vs. … versus.

Note: If serious or very serious, please give reasons for the classification (mandatory)

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Comments:

[a] *No blinding, no protocol, no ITT; high dropout rate, no sensitivity analysis; no blinding in measurement of the outcome.*

[b] *Based on self-calculated mean difference between study group/relative risk.*

[c] *Counts were not reported. Data was presented in a box plot and was extracted using the WebPlotDigitizer software[103].*
It is important to note that data may contain inaccuracies and should be treated with caution. In addition to mean values, only maximum values (max.) are shown in the graph.

[d] *Small sample size.*

[e] *low number of events.*

[f] *Broad confidence interval.*

[g] *Narrow confidence interval.*

[h] *Statistical power < 80%.*

[i] *Exceeding the threshold for small effects (±10).*

[j] *Exceeding the threshold for moderate effects (±2).*

[k] *Exceeding the threshold for large effects (±3).*

[l] *Sample size < approximated OIS (Symptoms n=110-150, ADLs n=120, Sport/rec. n=150-170) based on α=0.05, β=0.20 (power=80%), MCID=10.*

[m] *Sample size < approximated OIS of 40-48 participants based on α=0.05, β=0.20 (power=80%), MCID=25.*

[n] *Sample size < approximated OIS of 90-100 participants based on α=0.05, β=0.20 (power=80%), MCID=14.*

[o] *Sample size < approximated OIS of 72 participants based on α=0.05, β=0.20 (power=80%), SD=30 (conservative).*

[p] *Sample size < approximated OIS of 90-100 participants based on α=0.05, β=0.20 (power=80%), MCID=12.*

Table A-11: Evidence-profile AMIC+ versus MACI in patients with cartilage defects

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised I	N of pts randomised C	Effect	Certainty
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with IKDC objective; A=normal, B=nearly normal, C=abnormal, D=severely abnormal + IKDC subjective; 0-100, higher scores indicate better function)										
1	observational study	serious[a]	NA	not serious	very serious[m]	none	18	19	**Objective** (A/B/C/D, No.): 12A, 6B vs. 15A, 4B **Subjective** 74.67 (±13.90) vs. 81.05 (±8.31)	⨁◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with IKDC objective; A=normal, B=nearly normal, C=abnormal, D=severely abnormal + IKDC subjective; 0-100, higher scores indicate better function)										
1	observational study	serious[a]	NA	not serious	very serious[m]	none	18	19	**final FU mean 56.9**[b] **Objective (A/B/C/D, No.)**: 14A, 4B vs. 10A, 8B, 1C, p=0.12 **Subjective:** 82.52 (±10.72) vs. 75.70 (±9.85), **p=0.015**	⨁◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with KOOS; 0-100, higher scores indicate fewer symptoms/better function)										
1	observational study	serious[a]	NA	not serious	very serious[k]	none	18	19	**Symptoms** 84.94 (±11.92) vs. 86.05 (±9.47) **ADLs** 88.67 (±10.90) vs. 85.94 (±13.66) **Sport/rec** 68.78 (±23.36) vs. 71.42 (±14.16)	⨁◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with KOOS; 0-100, higher scores indicate fewer symptoms/better function)										
1	observational study	serious[a]	NA	not serious	very serious[k]	none	18	19	**final FU=mean 56.9**[b] **Symptoms** 90.61 (±10.85) vs. 81.05 (±11.04), p=0.430 **ADLs** 92.11 (±9.02) vs. 82.15 (±11.29), p=0.461 **Sport/rec** 79.72 (±17.37) vs. 68.84 (±15.25), p=0.173	⨁◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with TAS; 0-10, higher score indicates higher activity level)										
1	observational study	serious[a]	NA	not serious	very serious[l]	none	18	19	5.61 (±1.41) vs. 5.57 (±0.83)	⨁◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with TAS; 0-10, higher score indicates higher activity level)										
1	observational study	serious[a]	NA	not serious	very serious[l]	none	18	19	**final FU mean 56.9**[b] 6.05 (±1.10) vs. 5.26 (±1.14), p=0.220	⨁◯◯◯ very low
Quality of life: Improvement from baseline (FU ≤24 months, assessed with KOOS QoL; 0-100, higher scores indicate better QoL)										
1	observational study	serious[a]	NA	not serious	very serious[m]	none	18	19	76.0 (±18.5) vs. 79.3 (±15.1)	⨁◯◯◯ very low
Quality of life: Improvement from baseline (FU >24 months, assessed with KOOS QoL; 0-100, higher scores indicate better QoL)										
1	observational study	serious[a]	NA	not serious	very serious[m]	none	18	19	**final FU mean 56.9**[b] 84.0 (±14.8) vs. 76.1 (±16.9), p=0.107	⨁◯◯◯ very low

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised		Effect	Certainty
							I	C		
Pain: reduction from baseline (FU ≤24 months, assessed with VAS; 0-10, lower scores indicate less pain)										
1	observational study	serious[a]	NA	not serious	serious[n]	none	18	19	0.7 (±1.0) vs. 0.4 (±0.6)	⨁◯◯◯ very low
Pain: reduction from baseline (FU >24 months, assessed with VAS; 0-10, lower scores indicate less pain)										
1	observational study	serious[a]	NA	not serious	serious[n]	none	18	19	0.3 (±0.7) vs. 0.8 (±0.7), p=0.418	⨁◯◯◯ very low
Pain: reduction from baseline (FU ≤24 months, assessed with KOOS pain; 0-100, higher scores indicate less pain)										
1	observational study	serious[a]	NA	not serious	very serious[o]	none	18	19	90.3 (±10.2) vs. 83.3 (±10.6)	⨁◯◯◯ very low
Pain: reduction from baseline (FU >24 months, assessed with KOOS pain; 0-100, higher scores indicate less pain)										
1	observational study	serious[a]	NA	not serious	very serious[o]	none	18	19	**final FU mean 56.9**[b] 93.5 (±8.2) vs. 80.7 (±11.8)	⨁◯◯◯ very low
Structural repair: defect filling (assessed with %)										
1	observational study	not serious	NA	not serious	very serious[c, d]	none	18	19	**final FU mean 56.9**[b] Complete or near complete (>50%): 81% vs. 76% Complete Integration with adjacent cartilage: 93.7% vs. 88.2%	⨁◯◯◯ very low
Safety: adverse events (FU >24 months, assessed in % of pts)										
1	observational study	not serious	NA	not serious	serious[c, d]	none	18	19	**final FU mean 56.9**[b] No adverse reactions or postoperative infections were noted	⨁◯◯◯ very low

Abbreviations: ADL … activities of daily living; FU … follow-up; IKDC … International Knee Documentation Committee; KOOS … Knee Injury and Osteoarthritis Outcome Score; NA … not applicable; No. … number; pts … patients; QoL … quality of life; rec … recreation; SD … standard deviation (implied by the ± symbol); VAS … Visual Analog Scale; vs. … versus.

Note and Nomenclature for GRADE table *see Table A-10/page 111*

Comments:

[a] *No randomisation; Patients were aware of the intervention.*
[b] *Self-calculated mean over all pts. (AMIC+BMAC and MACI).*
[c] *Small sample size.*
[d] *low number of events.*
[e] *Broad confidence interval.*
[f] *Narrow confidence interval.*
[g] *Statistical power < 80%.*
[h] *Exceeding the threshold for small effects (±10).*
[i] *Exceeding the threshold for moderate effects (±2).*
[j] *Exceeding the threshold for large effects (±3).*
[k] *Sample size < approximated OIS (Symptoms n=110-150, ADLs n=120, Sport/rec. n=150-170) based on α=0.05, β=0.20 (power=80%), MCID=10.*
[l] *Sample size < approximated OIS of 40-48 participants based on α=0.05, β=0.20 (power=80%), MCID=25.*
[m] *Sample size < approximated OIS of 90-100 participants based on α=0.05, β=0.20 (power=80%), MCID=14.*
[n] *Sample size < approximated OIS of 72 participants based on α=0.05, β=0.20 (power=80%), SD=30 (conservative).*
[o] *Sample size < approximated OIS of 90-100 participants based on α=0.05, β=0.20 (power=80%), MCID=12.*

Table A-12: Evidence profiles AMIC+ versus MFx in patients with cartilage defects

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised I	N of pts randomised C	Effect	Certainty
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with IKDC objective; A=normal, B=nearly normal, C=abnormal, D=severely abnormal + IKDC subjective; 0-100, higher scores indicate better function)										
1	observational study	very serious[a]	NA	not serious	very serious[i]	none	27	25	**Objective (A/B/C/D, No.)** 16/9/0/0 vs. 4/12/9/0, **p<0.001** **Subjective, median (IQR)** 83 (15) vs. 80 (25), p<0.763	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with IKDC objective; A=normal, B=nearly normal, C=abnormal, D=severely abnormal + IKDC subjective; 0-100, higher scores indicate better function)										
1	observational study	very serious[a]	NA	not serious	very serious[i]	none	27	25	**60 months** **Objective (A/B/C/D, No.)** 19/6/0/0 vs. 2/5/13/5, **p<0.001** **Subjective, median (IQR)** 86 (14) vs. 77 (26), p=0.086	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with KOOS; 0-100, higher scores indicate fewer symptoms/better function)										
1	observational study	very serious[a]	NA	not serious	very serious[e]	none	27	25	**60 months; median (IQR)**[b] **Symptoms** 90 (12) vs. 87 (23), p=0.060 **ADLs** 95 (20) vs. 95 (23), p=0.217 **Sport/rec** 85 (17) vs. 68 (37), **p=0.013**	⊕◯◯◯ very low
Quality of life: Improvement from baseline (FU >24 months, assessed with KOOS QoL; 0-100, higher scores indicate better QoL)										
1	observational study	very serious[a]	NA	not serious	very serious[i]	none	27	25	**60 months; median (IQR)**[b] 85 (20) vs. 80 (39), p=0.289	
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with TAS; 0-10, higher score indicates higher activity level)										
1	observational study	very serious[a]	NA	not serious	very serious[h]	none	27	25	**median (IQR)**[b] 5 (1) vs. 5 (2), p=0.115	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with TAS; 0-10, higher score indicates higher activity level)										
1	observational study	very serious[a]	NA	not serious	very serious[h]	none	27	25	**60 months; median (IQR)**[b] 6 (1.5) vs. 4 (2), **p<0.001**	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU ≤24 months: assessed with Lysholm Score; 0-100, higher score indicates better knee function + fewer symptoms)										
1	observational study	very serious[a]	NA	not serious	not serious[k]	none	27	25	**median (IQR)**[b] 90 (25) vs. 90 (12), p=0.845	⊕◯◯◯ very low
Physical function/activity level/symptoms: improvement from baseline (FU >24 months: assessed with Lysholm Score; 0-100, higher score indicates better knee function + fewer symptoms)										
1	observational study	very serious[a]	NA	not serious	not serious[k]	none	27	25	**median (IQR)**[b] 90 (17) vs. 80 (20), p=0.178	⊕◯◯◯ very low

Certainty assessment							Summary of findings			
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of pts randomised		Effect	Certainty
							I	C		
Quality of life: Improvement from baseline (FU at ≤24 months assessed with KOOS QoL; 0-100, higher scores indicate higher QoL)										
1	observational study	very serious[a]	NA	not serious	very serious[i]	none	27	25	**60 months; median (IQR)**[b] 85 (20) vs. 80 (39), p=0.289	⨁◯◯◯ very low
Pain: reduction from baseline (FU >24 months, assessed with KOOS pain; 0-100, higher scores indicate less pain)										
1	observational study	very serious[a]	NA	not serious	very serious[j]	none	27	25	**60 months; median (IQR)**[b] 95 (10) vs. 87 (31), **p=0.023**	⨁◯◯◯ very low
Safety: adverse events (FU >24 months, assessed with % of pts)										
1	observational study	very serious[a]	NA	not serious	serious[c, d]	none	27	25	**60 months** No complications resulted from the procedure to harvest BMAC Stiffness requiring manipulation under anaesthesia 1 vs. 0	⨁◯◯◯ very low
Safety: severe adverse events (FU >24 months; assessed in % of pts)										
1	observational study	very serious[a]	NA	not serious	serious[c, d]	none	27	25	No serious adverse events	⨁◯◯◯ very low

Abbreviations: ADL … activities of daily living; BMAC … bone marrow aspirate concentrate; FU … follow-up; IKDC … International Knee Documentation Committee; IQR … interquartile range; KOOS … Knee Injury and Osteoarthritis Outcome Score; NA … not applicable; No. … number; pts … patients; QoL … quality of life; rec … recreation; vs. … versus.

Note: If serious or very serious, please give reasons for the classification (mandatory)

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Comments:

[a] *No adjustment for confounders; lost to FU excluded; non blinded assessment.*

[b] *IQR=Interquartile range (third quartile – first quartile).*

[c] *Small sample size.*

[d] *low number of events.*

[e] *Exceeding the threshold for small effects (±10).*

[f] *Sample size < approximated OIS (Symptoms n=110-150, ADLs n=120, Sport/rec. n=150-170) based on α=0.05, β=0.20 (power=80%), MCID=10.*

[h] *Sample size < approximated OIS of 56 participants based on α=0.05, β=0.20 (power=80%), SD=20 (conservative).*

[i] *Sample size < approximated OIS of 90-100 participants based on α=0.05, β=0.20 (power=80%), MCID=14.*

[j] *Sample size < approximated OIS of 90-100 participants based on α=0.05, β=0.20 (power=80%), MCID=12.*

[k] *required statistical power achieved.*

Applicability table

Table A-13: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	**AMIC** No applicability concerns were identified. Enrolled patients were aged between 18 and 68 years, with mean ages ranging from 34 to 49 years (IG) and 35 to 52 years (CG). Gender distribution varied considerably (11-73.3% female in IG, 23.1-79.6% in CG). Patients had cartilage defects ICRS grade IIIa or IV, with defect sizes ranging from 0.5 to 9cm^2. BMI was comparable between groups (24.7-27.9kg/m^2). If reported, defects were located on the femoral condyle, trochlea, patella, or on multiple areas. **AMIC+** No applicability concerns were identified, but some issues should be considered with caution. The average age ranged from 30 to 47 years in IG and 30 and 43.1 years in CG. Patients older than 60 years where not available and results for this age group may not be applicable. The participants in the trials were people with ICRS grade III to IV cartilage lesions that required surgical cartilage repair. In particular, the femoral condyle and the patellofemoral region were the most common sites of lesion. However, the results for these patient groups are not necessarily applicable to people with lesions in other locations such as the trochlea or patella.
Intervention	**AMIC** No applicability concerns were identified. AMIC was primarily performed via mini arthrotomy or arthroscopy. Six of seven studies included microfracture/debridement before scaffold insertion. Various scaffold products were used (e.g., Agili-c- implant, Chondro-Gide, Chondrotissue, CartiFill, MaioRegenTM, BST-Cargel) and could be inserted in different ways (sutured, glued, press-fit, injected). Postoperative rehabilitation protocols varied in weight. Bearing restriction and progression timelines, though all included comprehensive physical therapy **AMIC+** Applicability concerns were not identified. The main difference from the standard of care is the use of BMAC in addition to the AMIC technique (see above). All studies used BMAC harvested from the same site. The scaffolds used varied between trials, from a collagen type I/III bilayer matrix to various acid-based scaffolds. The fixation partly differed between studies.
Comparators	**AMIC** Six studies used microfracture alone as comparator, performed arthroscopically with special drills or awls. One study compared AMIC to ACI, involving a two-step procedure with chondrocyte harvesting, cultivation (3-4 weeks), and subsequent insertion under a collagen patch. These reflect standard treatment options for cartilage defects. Both comparators are considered standard of care in Austria. No applicability concerns were identified **AMIC+** Although no applicability concerns were identified, it should be noted that one study used the AMIC standard as a comparator, which is not yet considered the standard of care in Austria. In two other studies, MFx and MACI were selected as comparators; both of these are standard practices within Austrian clinical settings.
Outcomes	**AMIC** No applicability concerns were identified. Most studies reported physical function, activity level, symptoms, pain, structural repair, quality of life and adverse events, using valid measurement instruments. Especially the KOOS and IKDC were used for physical function and the VAS for pain. Structural repair was assessed through MRI interpretation. The majority of studies reported results at 24 months follow-up, two studies also reported 60 months follow-up, and one study for 120 months. Clinical benefits comprise reduced symptoms (e.g. pain and stiffness) and increased QoL. In some cases, adverse events occurred, however, they were comparable between groups. **AMIC+** No applicability concerns were identified. The outcomes of physical function, activity, symptoms, pain, structural repair and quality of life were reported in most of the studies at 24 months follow-up and long-term at 60 to partly 100 months follow-up. Considering that the main purpose of the intervention is to repair cartilage, to reduce symptoms and increase quality of life, these outcomes are appropriate. The occurrence of adverse events and re-operation was reported in most studies, but no study reported the necessity of joint replacement.
Setting	**AMIC** Studies were primarily conducted in Europe (Italy, Germany, Norway, Sweden, Austria, Switzerland, Belgium, Spain and Poland), one study also had participating clinics in South Africa, another study in Canada and South Korea, while one study was conducted in South Korea only. The results are applicable to the Austrian population. **AMIC+** All studies were conducted in Italy. Results are accordingly applicable to Austria. Therefore, there is no doubt concerning the applicability of the results.

Ongoing Trials

Table A-14: List of ongoing randomised controlled trials

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Endpoint	N of pts	Study completion date	Sponsor
NCT05651997	Pts with large cartilage defects in patellofemoral and femorotibial injuries	AMIC	MACT	KOOS	80	2032-06-01	Centre Hospitalier Universitaire Vaudois
NCT04840147	Pts with symptomatic focal articular cartilage lesions in the knee	Jointrep®+ Mfx	Mfx	Percentage of lesion fill measured by 3D quantitative Magnetic Resonance Imaging	185	2025-12	Oligo Medic Pty Ltd
NCT06576583	Pts with patellofemoral osteoarthritis	Engineered cartilage graft (N-TEC)	AMIC	KOOS pain	150	2030-01	University Hospital, Basel, Switzerland
NCT02539030	pts with cartilage defects in their knees	MFx	modified microfracture using collagen (CartiFill)	VAS Score	100	2017-06	Sewon Cellontech Co., Ltd.

Abbreviations: AMIC … Autologous Matrix-Induced Chondrogenesis; MACT … Matrix-Assisted Autologous Chondrocytes Transplantation; KOOS … Knee injury and Osteoarthritis Outcome Score; MFx … microfracture; VAS … Visual Analog Scale

Table A-15: List of ongoing randomised controlled trials of AMIC+

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Endpoint	N of pts	Study completion date	Sponsor
NCT02659215	Pts with symptomatic cartilage defects of the knee	Hyalofast with BMAC	Microfracture	KOOS pain score, IKDC subjective	200	2026-06-30	Anika Therapeutics, Inc.

Abbreviations: BMAC … Bone Marrow Aspirate Concentrate; IKDC … International Knee Documentation Committee; KOOS … Knee Injury and Osteoarthritis Outcome Score; N … Number; pts … patients

Research questions

Table A-16: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-17: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-18: Clinical Effectiveness

Element ID	Research question
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?

Table A-19: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0007	Are the technology and comparator(s) associated with user-dependent harms?

Literature search strategies

Search strategy for Cochrane

Search Name: AMIC for Cartilage Disorders in the Knee	
Search date: 19.12.2024	
ID	Search
#1	MeSH descriptor: [Cartilage Diseases] explode all trees
#2	((cartilage or osteo?chondr* or osteo-chondr* or chondr*) near (damage* or disorder* or defect* or lesion* or disease* or tear* or frissure*)) (Word variations have been searched)
#3	MeSH descriptor: [Cartilage, Articular] explode all trees and with qualifier(s): [abnormalities - AB, injuries - IN, pathology - PA, physiology - PH, physiopathology - PP]
#4	#1 or #2 or #3
#5	MeSH descriptor: [Knee Joint] explode all trees
#6	(Knee*) (Word variations have been searched)
#7	MeSH descriptor: [Knee Injuries] explode all trees
#8	MeSH descriptor: [Knee] explode all trees
#9	#5 or #6 or #7 or #8
#10	#4 and #9
#11	MeSH descriptor: [Osteochondritis Dissecans] explode all trees
#12	(osteo?chondritis dissecans) (Word variations have been searched)
#13	OCD:ti,ab,kw (Word variations have been searched)
#14	#10 OR #11 OR #12 OR #13
#15	MeSH descriptor: [Chondrogenesis] explode all trees
#16	autologous near chondrogenes* (Word variations have been searched)
#17	Matrix-Induced Chondrogenesis (Word variations have been searched)
#18	(cell-free NEAR matri*) (Word variations have been searched)
#19	AMIC (Word variations have been searched)
#20	(osteo?chondral regenerat*) (Word variations have been searched)
#21	(OCD regenerat*) (Word variations have been searched)
#22	"bone marrow" NEAR (aspirate* OR concentrate*) (Word variations have been searched)
#23	(BMAC):ti,ab,kw
#24	(Chondro-G?ide) (Word variations have been searched)
#25	Chondrotissue (Word variations have been searched)
#26	Hyalofast (Word variations have been searched)
#27	MaioRegen (Word variations have been searched)
#28	(CaRes):ti,ab,kw
#29	(BST-CarGel*) (Word variations have been searched)
#30	(Gelrin*) (Word variations have been searched)
#31	(Merg):ti,ab,kw
#32	(Chondro?fill*) (Word variations have been searched)
#33	(Joint?Rep) (Word variations have been searched)
#34	(cartifill) (Word variations have been searched)
#35	(spherox) (Word variations have been searched)
#36	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
#37	#14 AND #36
#38	English:la
#39	German:la (Word variations have been searched)

#40	#38 OR #39
#41	#37 AND #40
#42	(conference proceeding):pt
#43	(abstract):so
#44	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#45	#42 OR #43 OR #44
#46	#41 NOT #45
Total hits: 32	

Search strategy for Embase

Search Name: AMIC for Cartilage Disorders in the Knee		
Search date: 19.12.2024		
No.	Query Results	Results
#60.	#58 NOT #59	720
#59.	#58 AND 'Conference Abstract'/it	179
#58.	#57 AND ([english]/lim OR [german]/lim)	899
#57.	#23 AND #56	918
#56.	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55	21,436
#55.	'spherox*'	46
#54.	cartifill*	10
#53.	'joint rep*':dn,df	13
#52.	chondro$filler*	14
#51.	merg:ti,ab	250
#50.	'gelrin*	13
#49.	'bst$car*	55
#48.	'bst-car*'	62
#47.	cares:df,dn	49
#46.	maioregen*	46
#45.	hyalofast*	28
#44.	'chondro-tissue*'	5
#43.	chondro*tissue*	31
#42.	'chondro$gide*'	141
#41.	'chondro-g$ide*'	131
#40.	'engineered cartilage graft'/exp	175
#39.	bmac:ti,ab	466
#38.	'bone marrow aspirat*':ti,ab,de,kw,lnk	17,878
#37.	'bone marrow aspirate concentrate'/exp	115
#36.	'bone marrow aspiration'/exp	3,480
#35.	#33 AND #34	1,098
#34.	matri*:ti,ab,de,kw,lnk	801,316
#33.	'autotransplantation'/exp	35,358
#32.	'ocd regenerat*':ti,ab,de,kw,lnk	6
#31.	'osteo$chondr* regenerat*':ti,ab,de,kw,lnk	348
#30.	('cell free' NEAR/5 matri*):ti,ab,de,kw,lnk	270
#29.	amic:ti,ab	545

#28.	(('matri*-induc*' OR 'matri*-appli*' OR 'matri*-associat*' OR 'matri*-assist*') NEAR/5 ('autologous chondrocyte*' OR implant* OR transplant*)):ti,ab,de,kw,lnk	701
#27.	(autologous NEAR/5 chondro$genes*):ti,ab,de,kw,lnk	292
#26.	#24 AND #25	18
#25.	'collagen'/exp/dd_dt,dd_ad	3,280
#24.	'chondrogenesis'/exp	14,128
#23.	#12 OR #22	26,997
#22.	#11 AND #21	5,777
#21.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #20	31,135
#20.	#19 AND ('epidemiology'/lnk OR 'etiology'/lnk OR 'surgery'/lnk)	616
#19.	osteopathy	4,658
#18.	osteopathies:ti,ab,de,kw,lnk	432
#17.	chondromalacia*:ti,ab,de,kw,lnk	2,327
#16.	'chondromalacia'/exp	866
#15.	chondropath*:ti,ab,de,kw,lnk	6,630
#14.	ocd:ti,ab	18,710
#13.	'osteo$chondritis dissecans':ti,ab,de,kw,lnk	3,987
#12.	#7 AND #11	26,652
#11.	#8 OR #9 OR #10	326,059
#10.	'knee injury'/exp	45,804
#9.	knee*:ti,ab,de,kw,lnk	320,962
#8.	'knee'/exp	103,079
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	111,955
#6.	'cartilage injury'/exp	4,820
#5.	'cartilage damage'/exp	28
#4.	'cartilage defect'/exp	45
#3.	'cartilage lesion'/exp	45
#2.	((cartilage OR osteo$chondr* OR chondr*) NEAR/5 (damage* OR disorder* OR defect* OR lesion* OR tear* OR fissure* OR disease*)):ti,ab,de,kw,lnk	38,144
#1.	'chondropathy'/exp	87,850
Total hits: 720		

Search strategy for Medline via Ovid

Search Name: AMIC for Cartilage Disorders in the Knee	
Search date: 18.12.2024	
ID	Search
#1	exp Cartilage Diseases/ (14375)
#2	((cartilage* or osteo?chondr* or osteo-chondr* or chondr*) adj5 (damage* or disorder* or defect* or lesion* or disease* or tear* or fissure*)).mp. (34392)
#3	exp *Cartilage, Articular/ab, in, pa, ph, pp [Abnormalities, Injuries, Pathology, Physiology, Physiopathology] (8379)
#4	1 or 2 or 3 (46676)
#5	exp Knee Joint/ (76338)
#6	Knee*.mp. (225188)
#7	exp Knee Injuries/ (32213)
#8	5 or 6 or 7 (230562)
#9	4 and 8 (14041)
#10	exp Osteochondritis Dissecans/ (1835)
#11	osteo?chondritis dissecans.mp. (2801)

#12	osteo-chondritis dissecans.mp. (0)
#13	OCD.mp. (13037)
#14	exp Osteochondrosis/ (1642)
#15	osteo?chondros*.mp. (2951)
#16	osteo-chondros*.mp. (13)
#17	chondropath*.mp. (414)
#18	chondromalacia*.mp. (1156)
#19	osteopathies.mp. (373)
#20	osteopathy.mp. (2528)
#21	(ab or in or ep or pa or ph or su).fs. (10781715)
#22	20 and 21 (542)
#23	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 22 (20717)
#24	9 or 23 (33244)
#25	exp Chondrogenesis/ (6820)
#26	exp *Collagen/ad, tu [Administration & Dosage, Therapeutic Use] (3236)
#27	25 and 26 (16)
#28	(autologous adj10 chondro?genes*).mp. (238)
#29	matrix-induced chondro?genes*.mp. (201)
#30	AMIC.mp. (473)
#31	(cell-free adj5 matri*).mp. (228)
#32	osteo?chondr* regenerat*.mp. (313)
#33	osteo-chondr* regenerat*.mp. (1)
#34	(bone marrow adj3 (aspirate* or concentrate*)).mp. (6154)
#35	BMAC.mp. (403)
#36	OCD regeneration.mp. (7)
#37	Chondro-Gide.mp. (50)
#38	Chondrotissue.mp. (8)
#39	Chondro-Tissue.mp. (2)
#40	Hyalofast.mp. (13)
#41	MaioRegen.mp. (20)
#42	CaRes.mp. (5054)
#43	BST-CarGel*.mp. (22)
#44	Gelrin?C.mp. (3)
#45	MeRG.ti,ab. (118)
#46	Chondrofiller.mp. (6)
#47	JointRep.mp. (1)
#48	Cartifill.mp. (2)
#49	27 or 28 or 29 or 30 or 32 or 34 or 35 or 36 or 37 or 38 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (12344)
#50	24 and 49 (357)
#51	limit 50 to (english or german) (352)
#52	remove duplicates from 51 (352)
Total hits: 352	

Search strategy for HTA-INAHTA

Search Name: AMIC for Cartilage Disorders in the Knee	
Search date: 19.12.2024	
ID	Search
4	(AMIC) OR ((autologous) AND (chondrogenes*)) OR (matrix-induced chondrogenes*),"1","2024-12-19T14:27:44.000000Z"
3	AMIC,"1","2024-12-19T14:27:25.000000Z"
2	(autologous) AND (chondrogenes*),"1","2024-12-19T14:27:19.000000Z"
1	matrix-induced chondrogenes*,"0","2024-12-19T14:27:14.000000Z"
Total hits: 1	

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