

Matrix-Associated Chondrocyte Implantation Is Associated With Fewer Reoperations Than Microfracture

Results of a Population-Representative, Matched-Pair Claims Data Analysis for Cartilage Defects of the Knee

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Background: Symptomatic cartilage defects of the knee are commonly surgically treated by microfracture (MFX) or matrix-associated chondrocyte implantation (M-ACI). Several randomized controlled trials have compared MFX and M-ACI, showing a tendency to lower reoperation rates for M-ACI, but results vary widely between studies.

Purpose: To compare reoperation rates after MFX and M-ACI in cartilage defects of the knee outside clinical trials in a representative sample of the population.

Study Design: Cohort study; Level of evidence, 3.

Methods: This study was based on anonymized, population-representative claims data of 4 million insured persons in Germany. Patients who underwent MFX or M-ACI for cartilage defects of the knee with a follow-up of 2 years were compared. The primary endpoint was the need for a reoperation, defined as a claim for a second surgical procedure from the same patient at the knee joint (27 procedure codes), meniscus and cartilage (35 procedure codes), or patella (102 procedure codes) or the need for knee replacement (11 procedure codes). Group comparisons were performed using log-rank tests, with a 2-sided P value of $<.05$ to indicate significance. For adjusted analysis, propensity score matching was applied. Age, sex, comedications, and comorbidities were used as matching parameters.

Results: A total of 6425 patients fulfilled the inclusion criteria: 6273 treated with MFX and 152 treated with M-ACI (mean age, 53 and 36 years, respectively). In the 2 years after treatment, 1271 patients in the MFX group needed a reoperation compared with 19 in the M-ACI group (20.3% vs 12.5%, respectively; $P = .0199$). For adjusted analysis after propensity score matching, 127 patients per group were analyzed. Their mean age was 37 years. At the end of the second follow-up year, 28 and 16 patients needed reoperations in the MFX and M-ACI groups, respectively (22.0% vs 12.6%, respectively; $P = .0498$).

Conclusion: This study used a representative sample of the population and a broad definition of a reoperation, thus expanding evidence from clinical trials. We found a significant advantage of M-ACI in reoperation rates 2 years after treatment. After adjusting for age, sex, comedications, and comorbidities, M-ACI still showed significantly lower reoperation rates after 2 years.

Keywords: microfracture; matrix-associated chondrocyte implantation; M-ACI; cartilage defects; claims data

Articular cartilage defects in the knee are caused, among other reasons, by accidents such as twisting or age-related degeneration.^{4,11,29} If these cartilage defects remain untreated, premature osteoarthritis can occur.^{1,2,6,10,17,24} Surgical procedures such as microfracture (MFX) and matrix-associated chondrocyte implantation (M-ACI) are available to restore function, to relieve pain, and to reduce the probability of secondary osteoarthritis.¹ MFX, a

marrow-stimulating procedure, is performed by drilling into the subchondral bone lamella, leading to blood and stem cells entering the defect area.²⁵⁻²⁷ In recent decades, MFX has been performed increasingly frequently, as it is a minimally invasive procedure that places less strain on patients.¹ However, beside the risk of weakening the subchondral structure, in some cases the quality of the regenerated tissue is insufficient, especially for larger lesions in patients with a higher level of activity.^{15,28}

While the first generation of autologous chondrocyte implantation (ACI) entailed open surgery, subsequent generations of M-ACI have used arthroscopic or miniarthrotomy

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techniques to introduce the membrane into the joint.² In a 2-step procedure, the patient's chondrocytes are extracted, cultured, and reimplanted.¹ In the context of the abovementioned problems of MFX, M-ACI might be a preferable treatment option.¹⁶

(M-)ACI has been compared with MFX in several clinical studies, including randomized controlled trials. In these clinical studies, the advantages of (M-)ACI over MFX were found with respect to pain and functionality outcomes,² improvement of the Knee injury and Osteoarthritis Outcome Score (KOOS),³ and the occurrence of adverse events.¹⁴

However, only a few studies have examined the effectiveness of both treatment options in terms of reoperation rates, and these studies have led to conflicting results. Considering reoperation rates within 36 months, 1 study showed that the need for subsequent surgery was less frequent in patients treated by ACI (3.9%) than in those treated by MFX (11.5%).²³ A systematic review analyzed 2 MFX studies, 6 (M-)ACI studies, and 3 comparative studies. It was pointed out that failure rates varied between 10.3% (n = 29 patients; mean follow-up, 6.7 years) and 23% (n = 40; mean follow-up, 5 years) for MFX. Failure rates varied between 7.1% (n = 42; mean follow-up, 96 months) and 26% (n = 111; mean follow-up, 56 months) for ACI–collagen membrane/ACI-periosteum, and it was 9.5% (n = 21; mean follow-up, 5 years) for M-ACI.¹⁹

To summarize, in several clinical studies, (M-)ACI has shown an advantage over MFX regarding the frequency of reoperations. The goal of the present observational study was to compare the reoperation rates of MFX and M-ACI for cartilage defects of the knee 2 years after treatment, and outside of clinical trials, in an anonymized, representative, and unbiased sample of the German population.

METHODS

This study was based on data previously acquired and did not involve any other use of human participants or animal subjects. No informed consent was required for register-based studies using fully anonymized data.

Study Design and Data Sources

This comparative observational study was based on data from an anonymized German health claims database including 4 million persons insured through the German statutory health insurance (SHI) program. The data set

included 5% of the German population covered by the SHI from January 1, 2012, to December 31, 2015 (index period). The data set was stratified by age and sex to the demographic structure of the German population. It contained information on patients' diagnoses, treatment settings (ie, inpatient and outpatient), type of surgical treatment, and patients' demographic data. The study design was predefined by a detailed analysis protocol following the recommendations of the German Society for Epidemiology.

Patient Eligibility and Follow-up

Included in this study were patients with at least 1 M-ACI or MFX procedure performed during the index period in an outpatient or inpatient setting. If M-ACI and MFX were performed in the same patient within the index period, the patient was assigned to the treatment group performed first.

MFX and M-ACI were defined by the following procedure codes used in Germany for the documentation of inpatient and outpatient treatments: 5-801.kh and 5-812.hh for M-ACI and 5-812.fh and 5-801.hh for MFX. Each patient had been evaluated for 2 years after his/her initial surgery. Only patients observed for at least 2 years were included.

Outcome Assessment

The primary endpoint was the need for a reoperation, defined as a claim for a second surgical procedure in the knee. A follow-up period of 2 years was chosen to compare results with those of a recent US claims data analysis⁵ and a German chart review,²² both also using a 2-year follow-up period.

Because inpatient reimbursement in Germany is based on diagnosis-related groups (DRGs), the exact coding of surgical procedures heavily influences the amount reimbursed. For this reason, it was decided to identify reoperations in a broad way to ensure that all further interventions in the knee were included. To identify relevant procedure codes for reoperations, the German classification of medical procedures, an adaptation of the International Classification of Procedures in Medicine published by the World Health Organization, was searched for 4 search strings: (1) knee joint (including alignment), (2) meniscus and cartilage, (3) patella, and (4) prosthesis and knee replacement. Reoperations were then assessed as the first claim of the following codes: surgery in the knee joint (27 procedure codes), meniscus and cartilage (35 procedure codes), or patella (102 procedure codes) or the need for knee

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Ethical approval was not sought for the present study.

TABLE 1
Patient Demographic Characteristics Before and After Matching^a

	Before Matching (Unadjusted Analysis)			After Matching (Adjusted Analysis)		
	M-ACI (n = 152)	MFX (n = 6273)	P Value ^b	M-ACI (n = 127)	MFX (n = 127)	P Value ^b
Age, mean ± SD, y	35.98 ± 11.14	53.04 ± 14.00	<.0001	36.84 ± 10.91	36.94 ± 10.86	.9417
Age, n (%)						
<30 y	49 (32.24)	477 (7.60)	<.0001	37 (29.13)	36 (28.35)	≥.9999
30-39 y	43 (28.29)	401 (6.39)	<.0001	34 (26.77)	36 (28.35)	.8884
40-49 y	45 (29.61)	1374 (21.90)	.0291	44 (34.65)	41 (32.28)	.7904
≥50 y	15 (9.87)	4021 (64.10)	<.0001	12 (9.45)	14 (11.02)	.8364
Sex, n (%)						
Female	60 (39.47)	2866 (45.69)	.0004	52 (40.94)	52 (40.94)	≥.9999
Male	92 (60.53)	3407 (54.31)		75 (59.06)	75 (59.06)	

^aM-ACI, matrix-associated chondrocyte implantation; MFX, microfracture.

^bFisher exact test for categorical variables and 2-sample *t* test for continuous variables.

replacement (11 procedure codes). Patients could have undergone reoperations of more than 1 kind in the follow-up period and could thus be counted more than once when each reoperation category was compared (although only once in the analysis of the need for “any” reoperation). Owing to data availability, reoperations were assessed on a quarterly basis starting in the quarter of index treatment, that is, the M-ACI or MFX procedure triggering study inclusion.

Statistical Analysis

To reduce selection bias and to limit the risk that unrelated surgical procedures in the follow-up period would influence the results, the 2 groups were risk adjusted to baseline by using a matched-pair approach. Risk adjustment was performed with a mix of direct matching and propensity score matching, as proposed by Rubin and Thomas,²¹ to effectively reduce potential confounders. The propensity score was estimated by using multivariate logistic regression (logit model). Thereby, the 20 most frequently prescribed concomitant medications (anatomic therapeutic chemical classification system) and comorbidities (International Classification of Diseases–10th Revision–German modification category) coded in the outpatient or inpatient (main and secondary diagnoses) setting within the index period were included as covariates in the logistic regression.

Risk factors used in direct matching, in addition to propensity score estimation, were defined as age, sex, and year of index treatment for the following reasons: (1) Age: in several reports, inferior clinical outcomes were reported for patients older than 40 years, and recommendations for elderly patients are not available.^{12,18} Further studies have pointed out that surgical procedures for cartilage defects are mostly performed on patients younger than 40 years.^{20,30} (2) Sex: isolated patellofemoral defects are more commonly diagnosed in female than male patients (24.3% vs 11.0%, respectively), whereas isolated medial defects are more common in male patients (21.2% vs 12.3%, respectively).¹³ (3) Year of index treatment: to

eliminate the influence of any possible change in reimbursement rules that could lead to different coding practices, patients were compared who were treated with M-ACI or MFX in the same year.

In the matching process, sex and year of index treatment were specified to fit exactly, whereas a difference of ±5 years in age was permitted (caliper). Estimated propensity scores were allowed to vary by ±0.2 SDs of propensity score estimation.

Group comparisons were performed using 2-sided log-rank tests with *P* < .05 to indicate statistical significance. Data were stored and analyzed by using Office Excel 2019 (Microsoft) and SAS (version 9.3; SAS Institute). The GenMatch algorithm was run with R, the free statistical software.

RESULTS

Unadjusted Analysis

Demographic and Clinical Characteristics. Before matching, 6425 patients met the inclusion criteria within the index period. Of these, 97.6% were in the MFX group (n = 6273), and 2.4% were initially treated with M-ACI (n = 152). The mean age of the MFX-treated patients was 53.04 ± 14.00 years, and that of the M-ACI-treated patients was 35.98 ± 11.14 years; 54.31% were male and 45.69% were female in the MFX group, versus 60.53% and 39.47%, respectively, in the M-ACI group (Table 1).

Reoperations. Within the first year after initial surgery, 12 of the 152 M-ACI-treated patients (7.9%) and 913 of the 6273 MFX-treated patients (14.6%) had to undergo a reoperation in the knee (*P* = .0189). Within 2 years after the initial intervention, 19 of 152 patients treated by M-ACI (12.5%) and 1271 of 6273 patients treated by MFX (20.3%) required a reoperation. The relative risk reduction for reoperations was 38% (95% CI, 5.7%-59.6%) for M-ACI compared with MFX, meaning that 13 patients needed to be treated by M-ACI, rather than MFX, to avoid 1 reoperation.

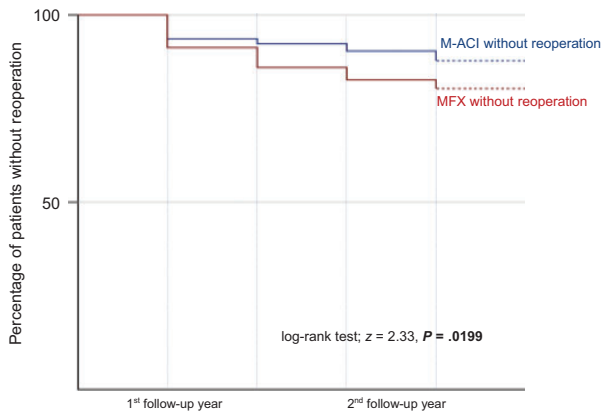


Figure 1. Unadjusted time-to-event analysis. M-ACI, matrix-associated chondrocyte implantation; MFX, microfracture.

This difference after 2 years was found to be statistically significant in favor of M-ACI in the time-to-event analysis ($z = 2.33; P = .0199$) (Figure 1). Reoperation procedures were distributed as follows in the MFX group (more than 1 reoperation per patient was possible): knee joint, $n = 775$ (12.35% of all patients); meniscus and cartilage, $n = 745$ (11.88%); patella, $n = 89$ (1.42%); and prosthesis and knee replacement, $n = 12$ (0.20%). Reoperation procedures were distributed as follows in the M-ACI group: knee joint, $n = 13$ (8.55%); meniscus and cartilage, $n = 13$ (8.55%); patella, $n = 0$ (0.00%); and prosthesis and knee replacement, $n = 0$ (0.00%).

Adjusted Analysis

Propensity Score Matching. The c value of the propensity score estimation was 0.85, indicating a good classification of the propensity scores.³¹ Thus, patients in the 2 matched groups (MFX and M-ACI) were well comparable.

Demographic and Clinical Characteristics. After matching, 127 patients, with a mean age of 36.84 ± 10.91 years in the M-ACI group and 36.94 ± 10.86 years in the MFX group, were included. In each group, 59.06% were male and 40.94% were female (Table 1). Patients did not differ significantly with respect to the 15 most common comorbidities or comedications (Table 2).

Reoperations. Within 1 year after index surgery, 16 of 127 MFX-treated patients (12.6%) had to undergo a reoperation, in contrast to 11 of 127 M-ACI-treated patients (8.7%) ($P = .4159$). Within 2 years after index surgery, a reoperation was necessary for 28 of the 127 MFX-treated patients (22.0%) and 16 of the 127 M-ACI-treated patients (12.6%). The relative risk reduction for reoperations was 43% (95% CI, 0%-67.5%) for M-ACI compared with MFX, resulting in a number needed to treat of 11 to prevent 1 reoperation.

This difference after 2 years was statistically significant in the time-to-event analysis ($z = 1.96; P = .0498$) in favor of M-ACI and was comparable with the results of the unadjusted analysis (Figure 2). Reoperation procedures were distributed as follows in the MFX group (more than 1

reoperation per patient was possible): knee joint, $n = 12$ (9.44%); and meniscus and cartilage, $n = 22$ (17.32%). Reoperation procedures were distributed as follows in the M-ACI group: knee joint, $n = 11$ (8.66%); and meniscus and cartilage, $n = 11$ (8.66%). Patella and knee replacement procedures were performed in fewer than 5 patients in each group; the exact number cannot be reported because of data protection regulations.

DISCUSSION

Within 2 years after index surgery, the relative risk for requiring reoperations was 38% lower in M-ACI-treated patients than in MFX-treated patients. After adjusting for age, sex, comorbidities, and comedications, the relative risk for requiring reoperations was 43% lower in the M-ACI group. Thus, MFX treatment led to statistically significantly more reoperations within 2 years after initial surgery when an adjustment was made for age, sex, comedications, and comorbidities.

An earlier retrospective analysis from 2018 based on the private US payer database PearlDiver examined “return to operating room” after MFX, ACI, osteochondral autograft transplantation, and osteochondral allograft transplantation within 90 days, 1 year, and 2 years after the initial cartilage treatment.⁵ From 2007 to 2011, a total of 640 ACI and 43,576 MFX procedures were performed and their results analyzed. After 2 years, 26.69% of the ACI-treated patients and 14.65% of the MFX-treated patients had to return to the operating room. The risk of reoperations after ACI was statistically significantly increased ($P < .0001$). The present study, in contrast, showed that reoperation rates were lower for M-ACI than for MFX after a 2-year observation period, even after adjusting for age, sex, and medical differences. The difference between these results might have been caused by the comparison with first-generation ACI. Furthermore, the study cited⁵ was based on Current Procedural Terminology codes, whereas in our study, German procedure codes were used to identify relevant patients for the study. The difference in procedure codes might be another reason for the contrasting results.

A systematic review¹⁵ published in 2009 that included 28 studies comprising 3122 MFX-treated patients (the mean number of patients per study was 110, with a mean follow-up time of 41 months) reported reoperation rates between 2.5% after 2 years and 31% at 2 to 5 years after initial surgery in the randomized studies examined. Several of the case studies reviewed showed reoperation rates between 2% and 7% at 4 to 11 years after MFX. According to the authors, the heterogeneity among the results might have been a result of differing methodological evidence levels in the studies reviewed, as the studies of higher methodological quality found higher reoperation rates.

A German study²² published in 2013 based on a retrospective chart review, including patient interviews with 454 consecutive MFX-treated patients and a follow-up period of at least 2 years, pointed out that there was a need for reoperations in 26.9% of MFX-treated patients. These findings are in line with the results from the present study,

TABLE 2
Clinical Results After Matching^a

	M-ACI (n = 127)	MFX (n = 127)	P Value ^b
Top 15 baseline comedications			
Anti-inflammatory and antirheumatic products (M01)	70 (55.12)	63 (49.61)	.4510
Antibacterials for systemic use (J01)	50 (39.37)	51 (40.16)	≥.9999
Antithrombotic agents (B01)	45 (35.43)	35 (27.56)	.2240
Analgesics (N02)	31 (24.41)	29 (22.83)	.8827
Drugs for acid-related disorders (A02)	25 (19.69)	21 (16.54)	.6253
Thyroid therapy (H03)	13 (10.24)	8 (6.30)	.3625
Psychoanaleptics (N06)	10 (7.87)	13 (10.24)	.6627
Drugs for functional gastrointestinal disorders (A03)	10 (7.87)	16 (12.60)	.3007
Agents acting on renin-angiotensin system (C09)	9 (7.09)	6 (4.72)	.5960
Drugs for obstructive airway diseases (R03)	9 (7.09)	10 (7.87)	≥.9999
Corticosteroids, dermatological preparations (D07)	8 (6.30)	18 (14.17)	.0608
Corticosteroids for systemic use (H02)	8 (6.30)	11 (8.66)	.6344
Beta-blocking agents (C07)	7 (5.51)	5 (3.94)	.7689
Cough and cold preparations (R05)	6 (4.72)	9 (7.09)	.5960
Psycholeptics (N05)	5 (3.94)	5 (3.94)	≥.9999
Top 15 baseline comorbidities			
Internal derangement of knee (M23)	83 (65.35)	75 (59.06)	.3651
Gonarthrosis (arthrosis of knee) (M17)	62 (48.82)	43 (33.86)	.0216
Other joint disorders, not elsewhere classified (M25)	58 (45.67)	57 (44.88)	≥.9999
Disorders of patella (M22)	49 (38.58)	46 (36.22)	.7954
Other disorders of cartilage (M94)	45 (35.43)	42 (33.07)	.7915
Dorsalgia (M54)	41 (32.28)	30 (23.62)	.1618
Dislocation, sprain, and strain of joints and ligaments of knee (S83)	34 (26.77)	43 (33.86)	.2747
Special screening examination for neoplasms (Z12)	33 (25.98)	29 (22.83)	.6614
Acute upper respiratory infections of multiple and unspecified sites (J06)	33 (25.98)	33 (25.98)	≥.9999
Contraceptive management (Z30)	27 (21.26)	28 (22.05)	≥.9999
Biomechanical lesions, not elsewhere classified (M99)	23 (18.11)	18 (14.17)	.4955
Disorders of refraction and accommodation (H52)	19 (14.96)	14 (11.02)	.4558
Essential (primary) hypertension (I10)	18 (14.17)	14 (11.02)	.5711
Other acquired deformities of limbs (M21)	18 (14.17)	19 (14.96)	≥.9999
Vasomotor and allergic rhinitis (J30)	17 (13.39)	15 (11.81)	.8503

^aData are shown as No. of patients (%). M-ACI, matrix-associated chondrocyte implantation; MFX, microfracture.

^bFisher exact test.

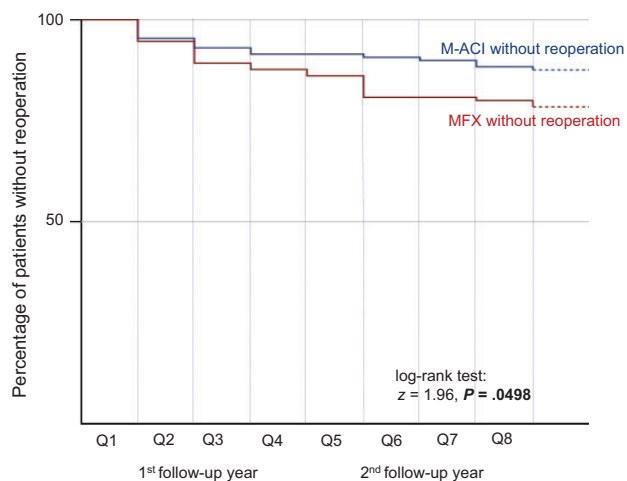


Figure 2. Adjusted time-to-event analysis. M-ACI, matrix-associated chondrocyte implantation; MFX, microfracture; Q, quarter.

which indicates a postoperative reoperation rate of 22.0% in MFX-treated patients after 2 years. The slight deviation in results might be because of selection bias, as patients had to give their informed consent to participate in the study cited. In contrast, our study was based on retrospective claims data without the requirement of patients' informed consent.

Furthermore, in a Norwegian randomized controlled trial⁹ published in 2007, a total of 40 MFX-treated and 40 ACI-treated patients were surveyed after 2 and 5 years. At 2-year follow-up, reoperation rates of 5% for ACI and 3% for MFX were found. The difference between these results and those of the present study might be caused by the comparison with ACI, as the present study compared MFX with next-generation M-ACI, and the Norwegian study imposed stricter inclusion and exclusion criteria, for example, regarding age, size of the defect, and requirement for informed patient consent.

Results from clinical studies have varied widely. This heterogeneity may be because varying inclusion criteria in clinical trials might have led to nonrepresentative study

populations. Furthermore, other uncertainties associated with trials, namely, the difficulty in reaching the minimum sample size to achieve the required 80% statistical power in clinical trials, the low acceptance rate of patients taking part in a surgical randomized controlled trial (patients might prefer a particular treatment option), and clinicians who are differently skilled in the interventions, might further limit the external validity of clinical trial results.⁸

Implications for Further Research and Practice

This study showed that M-ACI led to fewer reoperations compared with MFX within the first 2 years after treatment. These results, based on real-world clinical data, were partly in line with and partly in contrast to results of clinical studies. In 2016, in Germany, about 3000 M-ACI and 60,000 MFX procedures were performed (extrapolated from the 5% sample).⁷ If one takes into account the difference in reoperation rates after matching (M-ACI: 12.6%; MFX: 22.0% [ie, a difference of ~9%]), then MFX can be calculated to lead to 5400 additional reoperations per year compared with M-ACI. Reoperations for MFX might especially occur in extensive lesions, a factor that we could not include in our analysis and which needs further research.

As this study was based on real-world clinical data, in contrast to earlier clinical trials, further research is needed to assess possible causes for the differences between the respective results. These might be found in insufficient patient compliance, questionable patient selection, or varying physicians' skills.

Strengths and Limitations

The main strength of this study was that it reflects unaltered results on the efficacy of both treatments, as it used real-world clinical data. Additionally, selection bias was minimized with a broad risk adjustment of patients by means of propensity score matching. This baseline matching not only minimized selection bias, it also reduced the risk that observed differences in surgical procedures in the follow-up period were unrelated to the index surgery: In a comparison of patients with a similar risk profile, one would expect surgical procedures unrelated to the index treatment to be distributed equally across the groups. Finally, the database used was a population-representative sample, thus leading to a high external validity of results.

This study had the following limitations. Because it relied on procedure codes to identify reoperations, we were not able to attribute them directly to the initial surgery. Because the baseline characteristics of the patients were matched as closely as possible in the adjusted analysis, one would expect further surgical procedures, that is, those not related to the initial intervention, to be distributed equally between the 2 treatment groups and not to affect the results; nevertheless, uncertainties remain, given the broad definition of reoperations in this study. To overcome those uncertainties, further real-world clinical data research is required, ideally with detailed patients' records, from which the reasons for second and third surgical

procedures can be evaluated and their relationship to the initial surgery can be assessed.

The analyses were based on claims data that are also used to set the amount reimbursed for the clinics and physicians involved. Thus, diagnoses and surgery data might not only reflect medical indications but could also be influenced by reimbursement optimization ("upcoding"). To reduce this risk, diagnoses were not taken into account in the eligibility criteria, as they were considered to be significantly influenced by different extents of reimbursement in the German DRG payment system. Thus, as indications between M-ACI and MFX vary and are stricter for M-ACI, groups might not be fully comparable, despite the propensity score matching approach. Furthermore, results may be further biased if one of the procedures was only coded for reimbursement purposes and was not performed in clinical practice.

This study used a follow-up period of 2 years to compare results with those of other recent claims data analyses. The present analysis cannot answer the question of whether the differences observed between M-ACI and MFX persist over a longer follow-up period.

Patients insured by private health insurance companies (~10% of the German population) were not included in this study. Furthermore, the study was restricted to reoperation rates and did not include any statements regarding the functionality of the knee after the intervention. An earlier study showed that M-ACI-treated patients experienced statistically significantly higher levels of functionality after 5 years than did MFX-treated patients.² Patients may have a more functional knee, despite having a statistically significant chance of a reoperation. Moreover, the extent of the damage (assessed either by the KOOS or by lesion size) was not known in the present study.

CONCLUSION

This study, based on unselected claims data of a population-representative sample, showed that M-ACI has advantages compared with MFX regarding reoperation rates within 2 years after initial surgery. This advantage was still seen after adjusting for age, sex, comedications, and comorbidities. M-ACI seems to be a more effective treatment option than MFX for cartilage defects of the knee. In Germany, MFX could lead to an important number of additional reoperations compared with M-ACI.

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