Systematic Review

Revision Surgery Is the Most Common Definition of Failure in Studies Evaluating Knee Cartilage Restoration Outcomes: A Systematic Review

Lexy Farrington, B.S., Marcus Trotter, M.D., Ezra Goodrich, M.D., Armin Tarakemeh, B.A., Erik Henkelman, M.D., Paul Schroeppel, M.D., Christopher D. Bernard, M.D., Rachel Long, B.S., Tucker Morey, B.S., Jacob White, M.S., and Bryan G. Vopat, M.D.

Purpose: To assess the definitions of "failure" of knee chondral restoration surgery in the current literature and to provide a recommendation on what should define failure. **Methods:** By use of Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria, a systematic search of the PubMed, Embase, Ovid, and Cochrane Library databases was conducted to identify studies published between January 1, 2017, and May 1, 2021. The inclusion criteria consisted of studies containing patients who underwent knee cartilage surgery that included a definition of failure. We excluded animal studies; articles comparing alternative medical treatments, such as rehabilitation, anti-inflammatory medications, and physical therapy; studies enrolling patients with diseases other than those of the knee, and non—English-language studies. Failure data were extracted and categorized as surgical, graft related, or based on patient-reported outcomes (PROs). This information was analyzed to develop a recommendation for a standardized definition of failure of knee cartilage restoration. **Results:** A total of 61 studies met the inclusion criteria. The most common definition of knee chondral restoration failure was the need for any revision surgery (52 of 61 studies, 85.3%), with failure rates ranging from 3.22% to 75%. Graft failure, defined as delamination and/or graft inadequacy (39 of 61, 63.9%), with failure rates ranging from 2.10% to 47%, and conversion to knee arthroplasty (34 of 61, 55.7%) were also used as definitions. Failure to return to sport and/or regular activity (4 of 61, 6.6%), presence of symptoms (21 of 61, 34.4%), removal of graft or implant (14 of 61, 22.9%), and other unclassified follow-up revisions (8 of 61, 13.1%) were additional definitions of failure documented. Subjective PROs were used in 54.1% of the studies (33 of 61), with failure rates ranging from 3.45% to 59%. **Conclusions:** A variety of definitions of failure are used to evaluate knee chondral restorative surgery outcomes in the orthopaedic literature. Any unplanned revision surgery and graft failure, defined as delamination and/or graft inadequacy, were the most common criteria defining knee chondral restoration failure. Patients' functionality and quality of life, determined by PROs, were also used to define knee chondral restoration failure in multiple studies. Higher rates of failure were observed after knee chondral restorative procedures when using multiple definitions of failure that were more inclusive. To account for heterogeneity in definitions, procedures, and patient circumstances, we recommend using multiple outcomes, including unplanned surgical procedures, PROs, and the ability to return to the desired level of function, as factors to define failure. **Level of Evidence:** Level IV, systematic review of Level II to IV studies.

Knee chondral defects are a common yet challenging pathology seen by orthopaedic surgeons. With approximately 750,000 arthroscopic knee operations each year, chondral lesions are found in nearly 60% of knee arthroscopies performed.[1,2] At the same time, knee chondral defects are 20% more common in athletes.[3,4] Knee chondral defects can be treated in a conservative or surgical manner. Surgical management of knee chondral defects consists of palliation, repair, or restoration and includes a wide variety of surgical techniques, including but not limited to chondroplasty, microfracture, autologous chondrocyte implantation (ACI), osteochondral autograft transfer (OAT), and osteochondral allograft. These procedures seek to conserve patients' native tissue, and a standard definition of "failure" facilitates comparison between these

From the Department of Orthopedic Surgery and Sports Medicine, University of Kansas Medical Center, Kansas City, Kansas, U.S.A.

Received June 9, 2024; accepted November 3, 2024.

Address correspondence to Christopher D. Bernard, M.D., Department of Orthopedic Surgery and Sports Medicine, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, U.S.A. E-mail: cbernard2@kumc.edu

2666-061X/24375

https://doi.org/10.1016/j.asmr.2024.101044

procedures and their outcomes. Whereas diversity in knee chondral surgical techniques provides considerable options for surgeons in treating knee chondral defects, the use of varied definitions of failure limits the ability of researchers to compare these procedures. The breadth of surgical techniques leading to different mechanisms of failure further complicates the issue.

A previous systematic review showed that included studies only reported outcome results for singular knee chondral surgical techniques but did not analyze or provide a universal standard for the definition of failure across all knee chondral restoration surgical techniques.[5] A meta-analysis revealed that multiple studies have examined knee chondral restoration surgical techniques and used failure rates to determine what technique is statistically "best" to treat knee chondral defects in patients, despite lack of standardization of the term "failure."[4]

Given the complexity of knee chondral injuries, the variety of surgical techniques for knee chondral defects, and the magnitude of knee chondral procedures performed, a universal definition of failure for general knee chondral restoration outcomes is necessary. The purposes of this study were to assess the definitions of "failure" of knee chondral restoration surgery in the current literature and to provide a recommendation on what should define failure. We hypothesized that studies of patients who underwent knee chondral restoration procedures would have varying definitions of failure.

Methods

Literature Search

A systematic search of the PubMed, Embase, Ovid, and Cochrane Library databases was conducted by a university librarian to identify studies related to knee chondral restoration failure. The search terms used included "knee cartilage restoration," "knee cartilage surgery," "knee chondral restoration," "knee cartilage repair," "microfracture," "chondroplasty," "ACI" or "autologous chondrocyte implantation," "articular cartilage restoration," "osteochondral autograft transfer," "OATS," "osteochondral allograft transplant," and "MACI" or "matrix-induced autologous chondrocyte implantation." Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used during this systematic review, and institutional review board approval was not required.

Study Eligibility Criteria

The inclusion criteria consisted of studies containing patients who underwent knee cartilage restorative surgery that included a definition of failure. All eligible studies were published in English between January 2017 and May 2021 and comprised Level II to IV evidence. We excluded articles comparing alternative medical treatments, such as rehabilitation, anti-inflammatory medications, and physical therapy; cadaveric studies; animal studies; and publications enrolling patients with diseases other than those of the knee. A knee chondral restorative procedure was defined as a surgical intervention that treated articular chondral lesions or defects. This included but was not limited to ACI, microfracture, OAT, osteochondral allograft transplantation, matrix-assisted autologous chondrocyte transplantation, and autologous cartilage transplantation. Concomitant procedures involved with the knee were also included in this review.

Study Selection and Data Extraction

Once all the studies from the aforementioned databases were identified, 2 research team members (L.F. and E.G.) independently screened each article's title using previously determined exclusion criteria. The remaining articles were subsequently screened by their abstracts. The full text of each qualifying article was then reviewed and either included or excluded from the final list. After each step, the respective lists of included and excluded articles were compared. If there was disagreement on inclusion, both team members would review the article again separately before meeting to discuss their reasoning, and a joint decision would be made to include or exclude the article. If there was still disagreement, a senior team member (E.H.) was consulted to make the final decision. Two team members (L.F. and E.G.) then divided the final list of included articles and extracted the data from each full-text publication. Failure data were extracted from each study and divided into the following categories: surgical (any revision, conversion to knee arthroplasty, and other knee cartilage procedures), graft failure (confirmed by imaging and second-look arthroscopy), and patient-reported outcomes (PROs) (lack of significant improvement, dissatisfaction or persistent pain, and inability to return to sport).

Risk-of-Bias Assessment

The quality of all included studies was evaluated by 2 independent authors (L.F. and R.L.) using the Methodological Index for Non-randomized Studies tool (Table 1). Disagreements would have been resolved by a third author (C.D.B.); however, no disagreements occurred. The scoring for each question is as follows: 0, not reported; 1, reported but insufficient; and 2, reported and sufficient. The maximal score is 24 points for a comparative study and 16 points for a non-comparative study.

Results

A total of 1,812 studies were identified and screened in the initial search (Fig 1). Of these studies, 61 (3.36%)

Table 1. Breakdown of Study Characteristics Including Surgical Technique, Number of Knees, Number of Failed Knees, Reported Failure Definition, and MINORS Score

Authors	Year	Type of Study/LOE	Surgical Technique	Failure Definition	Failure Rate, %	No. of Failed Knees/No. of Total Knees	Mean Follow-Up Time	MINORS Score
Barbieri Mestriner et al.[6]	2020	Cohort study/III	Patellofemoral ACI	Reoperation; removal of allograft; conversion to arthroplasty, confirmed by imaging and/or arthroscopy; poor integration of graft; PROs (KOOS, Lysholm score, TAS, IKDC score)	4.35	2/46	3.7 yr	20 of 24
Barié et al.[7]	2020	RCT/II	ACI, MACI	Reoperation, confirmed by imaging	56.25	9/16	9.6 yr	19 of 24
Di Martino et al.[8]	2021	Cohort study/III	OATS	Reoperation because of SXS due to primary defect and/or absence of clinically significant improvement in PROs, consisting of IKDC score (10 IKDC subjective points per literature definition with respect to basal evaluation)	25.93	7/27		16 of 24
Gomoll et al.[9]	2017	Cohort study/III	Cell-seeded ACI	Reoperation; removal of >25% of original defect size; graft failure, confirmed by imaging	15.48	13/84	3.275 yr	16 of 24
Hoburg et al.[10]	2021	RCT/II	ACI, microfracture	Reoperation	3.92	4/102	3 yr	21 of 24
Riff et al.[11]	2020	Cohort study/III	ACI, OAT, second-look arthroscopy	Reoperation, conversion to arthroplasty, persistent or recurrent SXS, graft delamination or grade IV chondrosis involving significant portion of graft site on second-look arthroscopy	10.03	36/359	2.72 yr	16 of 24
Pike et al.[12]	2017	Case series/IV	ACI plus some cases of concomitant ACL reconstruction	Reoperation, graft delamination, conversion to arthroplasty, no clinical improvement based on PROs (MCRS, WOMAC score, VAS score)	30.77	8/26		9 of 16
Teo et al.[13]	2019	Cohort study/III	ACI plus some cases of concomitant HTO	Reoperation, conversion to arthroplasty	12.50	9/72	10.75 yr	19 of 24
Roffi et al.[14]	2020	Case series/IV	ACT combined with autologous bone grafting	Reoperation owing to SXS due to primary defects, conversion to arthroplasty, no clinical improvement based on PROs (IKDC score [10 IKDC subjective points per literature definition with respect to basal evaluation], TAS)	15.79	3/19		14 of 16
von Keudell et al.[15]	2017	Case series/IV	ACI plus some cases of concomitant TTO, lateral tissue release, and trochleoplasty	Reoperation; structural failure, confirmed by imaging and/or arthroscopy	10.00	3/30	7.33 yr	10 of 16
Cole et al.[16]	2021	Cohort study/III	Microfracture	Graft delamination, confirmed by imaging and/or arthroscopy	2.08	1/48	2 yr	14 of 16
Johnson et al.[17]	2017	Case series/IV	OCA plus some cases of concomitant ACL reconstruction and partial medial and/or lateral meniscectomy	Reoperation; removal of implant; graft inadequacy; conversion to arthroplasty, confirmed by imaging and/or second-look arthroscopy	29.41	10/34	1.4 yr	11 of 16

(continued)

Table 1. Continued

Authors	Year	Type of Study/LOE	Surgical Technique	Failure Definition	Failure Rate, %	No. of Failed Knees/No. of Total Knees	Mean Follow-Up Time	MINORS Score
Ibarra et al.[18]	2021	RCT/II	MACT, microfracture, second-look arthroscopy plus some cases of concomitant ACL reconstruction and meniscal repair	Reoperation because of SXS caused by primary defect, tissue detachment and/or absence, PROs (SXS)	8.33	4/48	6 yr	20 of 24
Cinats et al.[19]	2021	Case series/IV	OCA	Reoperation, confirmed by imaging and/or second-look arthroscopy; PROs (SXS)	11.76	2/17	2 yr	10 of 16
Anderson et al.[20]	2018	Cohort study/III	OCA	Reoperation, removal of allograft, graft inadequacy, conversion to arthroplasty	3.75	3/80	3.71 yr	16 of 24
Martinčič et al.[21]	2019	Case series/IV	ACI plus some cases of concomitant ACL reconstruction and osteotomy	Reoperation; graft failure, confirmed by imaging and/or arthroscopy; conversion to arthroplasty	12.77	18/141	10 yr	11 of 16
Thomas et al.[22]	2019	Case series/IV	OCA plus some cases of concomitant osteotomy	Inability to return to sport, reoperation, conversion to arthroplasty, PROs (VAS score, SXS [persistent pain])	42.62	26/61	3.84 yr	10 of 16
Wang et al.[23]	2019	Case series/IV	OCA plus some cases of ACL reconstruction, osteotomy, and meniscal transplantation	Reoperation; removal of allograft; conversion to arthroplasty; graft inadequacy, confirmed by second-look arthroscopy	16.13	5/31	4.1 yr	10 of 16
Wang et al.[24]	2021	Cohort study/III	Mosaicplasty, OCA plus some cases of ACL reconstruction, osteotomy, and partial meniscectomy and/or repair	Reoperation; removal of allograft; conversion to arthroplasty, confirmed by imaging; graft inadequacy; poor PROs (IKDC score, KOOS, Marx activity rating, Cincinnati knee rating system)	18.58	21/113	4.5 yr	10 of 16
Solheim et al.[25]	2020	Cohort study/III	Microfracture, mosaicplasty	PROs (poor Lysholm score, <65 points [at 1-year follow-up or later]), conversion to arthroplasty, reoperation	62.07	126/203	12 yr	17 of 24
Solheim et al.[26]	2018	Case series/IV	Microfracture, mosaicplasty	Reoperation, conversion to arthroplasty	11.22	23/205	14 yr	11 of 24
Solheim et al.[27]	2019	Cohort study/III	Mosaicplasty	PROs (poor Lysholm score, <65 points), conversion to arthroplasty, reoperation	51.19	43/84	4 yr	19 of 24
Blanke et al.[28]	2021	Case series/IV	ACT	Reoperation; removal of tissue; tissue inadequacy; SXS and pain on follow-up physical examination, confirmed by imaging (low MOCART score); PROs (persisting pain); conversion to arthroplasty; focal articular prosthetic resurfacing	3.45	1/29	2.08 yr	11 of 24
Balazs et al.[29]	2018	Case series/IV	OCA	Reoperation; removal of graft; graft inadequacy; conversion to arthroplasty, confirmed by imaging	18.18	2/11	10.7 mo	8 of 16

(continued)

Table 1. Continued

Authors	Year	Type of Study/LOE	Surgical Technique	Failure Definition	Failure Rate, %	No. of Failed Knees/No. of Total Knees	Mean Follow-Up Time	MINORS Score
Merkely et al.[30]	2021	Cohort study/III	OCA (revision vs primary)	Reoperation; failure of >25% of graft; conversion to arthroplasty, confirmed by imaging and/or arthroscopy; additional surgical MST	15.38	4/26	2.1 yr	16 of 24
Ackermann et al.[31]	2020	Case series/IV	ACI plus some cases of concomitant osteotomy	Reoperation; failure of >25% of graft, confirmed by imaging and/or arthroscopy; conversion to arthroplasty	15.79	27/171	8.45 yr	10 of 16
Beck et al.[32]	2018	Cohort study/III	ACI	Reoperation; graft inadequacy; PROs (SXS on physical examination), confirmed by second-look arthroscopy; conversion to arthroplasty, general non-healing and/or loose bodies	40.00	4/10	12 yr	10 of 16
Kim et al.[33]	2019	Case series/IV	Microfracture plus some cases of concomitant meniscectomy	Reoperation; conversion to arthroplasty, confirmed by imaging; HTO	5.63	4/71	7.2 yr	9 of 16
Carey et al.[34]	2020	Case series/IV	ACI; second-look arthroscopy	Reoperation; conversion to arthroplasty; failed fixation with drilled pins; failure to improve from baseline PROs (KOOS, Lysholm score), confirmed by second-look arthroscopy; violation of subchondral bone	18.18	10/55	19 yr	12 of 16
Stannard and Cook[35]	2020	Cohort study/III	OCA plus some cases of concomitant ACL reconstruction, TTO, HTO, and DFO	Reoperation; conversion to arthroplasty, confirmed by imaging	13.40	26/194	2.5 yr	18 of 24
Ebert et al.[36]	2017	Cohort study/III	Tibiofemoral or patellofemoral MACI plus some cases of concomitant ACL reconstruction, PCL reconstruction, partial meniscectomy, and HTO	No discernible tissue; graft hypertrophy; clinically symptomatic based on PROs (KOOS, pain, general symptoms), confirmed by imaging	8.76	17/194	2 yr	18 of 24
Ebert et al.[37]	2017	Case series/IV	MACI	Graft delamination, confirmed by imaging	6.45	2/31	5 yr	11 of 16
Ebert et al.[38]	2021	Case series/IV	MACI	Graft delamination, confirmed by imaging	9.09	9/99	13.1 yr	13 of 16
Ebert et al.[39]	2019	Cohort study/III	MACI	Graft delamination, confirmed by imaging	8.33	5/60	10 yr	18 of 24
Ebert et al.[40]	2020	RCT/II	MACI	Reoperation; conversion to arthroplasty; graft delamination, confirmed by imaging	9.38	6/64	10 yr	22 of 24
Ebert et al.[41]	2017	RCT/II	MACI	Graft delamination, confirmed by imaging	29.73	11/37	8 wk	22 of 24

(continued)

Table 1. Continued

Authors	Year	Type of Study/LOE	Surgical Technique	Failure Definition	Failure Rate, %	No. of Failed Knees/No. of Total Knees	Mean Follow-Up Time	MINORS Score
Tjörnstrand et al.[42]	2018	RCT/II	Microfracture vs ACI plus some cases of concomitant mosaicplasty within 2 yr of surgery	Reoperation, confirmed by imaging; progression to OA	75.00	12/16	17 yr	15 of 24
Zellner et al.[43]	2017	Case series/IV	Bone augmentation combined with MACT plus some cases of concomitant drilling, microfracture, OCT, meniscal refixation, distal realignment of patella, ACL reconstruction, and HTO	Inadequate integration; PROs (SXS [limited ROM]), confirmed by imaging and/or arthroscopy	2.17	1/46	2 yr	10 of 16
Schüttler et al.[44]	2019	Case series/IV	Cell-free type I collagen scaffold for cartilage repair	Reoperation; SXS due to implant wear, confirmed by imaging; PROs (TAS, KOOS, IKDC score, VAS score)	17.86	5/28	5 yr	9 of 16
Yoon et al.[45]	2019	Cohort study/III	ACI	Reoperation; SXS (unrelieved); graft inadequacy, confirmed by imaging; PROs (poor results for Lysholm score [<65])	42.42	14/33		20 of 24
Andriolo et al.[46]	2021	Case series/IV	MACT	Reoperation; SXS due to primary defects; return to activity; graft inadequacy; conversion to arthroplasty, confirmed by imaging; PROs (IKDC score, EQ-VAS, TAS)	12.90	4/31		13 of 16
Andriolo et al.[47]	2020	Case series/IV	MACT plus some cases of concomitant meniscectomy, ACL reconstruction, loose body removal, PCL reconstruction, osteotomy, meniscal implant, meniscal suture, lateral release, and patellar realignment	Reoperation, PROs (SXS on physical examination), conversion to arthroplasty	15.04	17/113	15 yr	12 of 16
Andriolo et al.[48]	2019	Case series/IV	MACT plus some cases of concomitant HTO, loose body removal, microfracture, ACL reconstruction, lateral release, patellar realignment, meniscectomy, PCL reconstruction, and hardware removal	Reoperation; SXS; conversion to arthroplasty, confirmed by imaging; PROs without clinical improvement (10 IKDC subjective compared with baseline)	58.54	24/41	15 yr	13 of 16

(continued)

Table 1. Continued

Authors	Year	Type of Study/LOE	Surgical Technique	Failure Definition	Failure Rate, %	No. of Failed Knees/No. of Total Knees	Mean Follow-Up Time	MINORS Score
Tírico et al.[49]	2019	Case series/IV	OCA plus some cases of concomitant DFO, HTO, meniscal allograft, meniscal repair, diagnostic arthroscopy, hardware removal, lateral release, ligament reconstruction, loose body removal, and partial meniscectomy	Reoperation, removal, graft inadequacy	8.00	16/200	6.7 yr	11 of 16
Berruto et al.[50]	2017	Cohort study/III	ACI	Reoperation, confirmed by imaging; PROs (IKDC score, Tegner score, EQ-VAS)	28.13	9/32		11 of 16
Zarkadis et al.[51]	2017	Case series/IV	ACI plus some cases of concomitant osteotomy and ligament reconstruction	Reoperation, inability to return to active military duty, SXS, conversion to arthroplasty	45.05	41/91	4.99 yr	11 of 16
Müller et al.[52]	2020	Cohort study/III	ACI	Reoperation and/or partial graft insufficiency	15.00	26/40		18 of 24
Frank et al.[53]	2017	Case series/IV	OCA plus some cases of concomitant MAT, ligament reconstruction, HTO, and DFO	Reoperation; conversion to knee arthroplasty; graft inadequacy, confirmed by arthroscopy	13.33	24/180	2.5 yr	8 of 16
Siebold et al.[54]	2018	Case series/IV	ACI	Poor results on MOCART via imaging; other definition (i.e., no/little cartilage regeneration)	10.00	3/30		11 of 16
León et al.[55]	2019	Case series/IV	OCA and realignment osteotomy	Reoperation, removal of allograft, graft inadequacy, conversion to arthroplasty	23.33	14/60	11.4 yr	8 of 16
Zaffagnini et al.[56]	2019	Case series/IV	MACT	Reoperation, SXS due to primary defects, return to sport considered in evaluation	3.23	1/31		11 of 16
Saris et al.[57]	2021	Case series/IV	Cartilage repair with mesenchymal stromal cells	Reoperation; graft inadequacy, confirmed by imaging and/or arthroscopy; other definition (i.e., reinjection)	14.29	5/35	5.08 yr	10 of 16
Minas et al.[58]	2018	Cohort study/III	ACI	Reoperation; partial graft failure; conversion to arthroplasty; SXS (evident swelling and persistent pain), confirmed by Imaging and/or arthroscopy; PROs (Cincinnati knee rating system, WOMAC score, VAS score, Short Form 36 score, patient satisfaction survey)	26.83	11/41	11.75 yr	15 of 24
Ogura et al.[59]	2017	Case series/IV	ACI plus some cases of concomitant TTO, HTO, DFO, and ACL reconstruction	Reoperation; conversion to arthroplasty; PROs (SXS), confirmed by imaging and/or arthroscopy; graft delamination	37.50	9/24	20.6 yr	12 of 16

(continued)

Table 1. Continued

Authors	Year	Type of Study/LOE	Surgical Technique	Failure Definition	Failure Rate, %	No. of Failed Knees/No. of Total Knees	Mean Follow-Up Time	MINORS Score
Ogura et al.[60]	2020	Case series/IV	Arthroscopic examination, with removal of chondral fragments	Reoperation; removal of graft, confirmed by imaging	16.67	1/6		13 of 16
Ogura et al.[61]	2017	Case series/IV	ACI plus some cases of concomitant DFO, MAT, HTO, MCL repair, and TTO	Persistent/recurrent SXS, confirmed by imaging; graft delamination; removal of 25% of graft; reoperation; violation of subchondral bone	10.34	3/29	9.6 yr	10 of 16
Ogura et al.[62]	2018	Case series/IV	ACI plus some cases of concomitant TTO, HTO, and DFO	PROs (persistent/recurrent clinical SXS), confirmed by imaging and/or arthroscopy; graft delamination; removal of 25% of graft; reoperation; conversion to arthroplasty	20.69	12/58	8.3 yr	12 of 16
Ogura et al.[63]	2019	Case series/IV	ACI plus some cases of concomitant marrow stimulation technique, bone grafting, TTO, HTO, ACL reconstruction, MAT, removal of hardware, lateral release, and VMO advancement	Reoperation; conversion to arthroplasty for persistent or recurrent SXS, confirmed by imaging; graft delamination or inadequate fill; PROs (SXS)	27.96	26/93	11.2 yr	12 of 16
Wang et al.[64]	2018	Case series/IV	OCA, ACI, subchondral marrow stimulation	Reoperation; removal; conversion to arthroplasty, confirmed by imaging and/or arthroscopy; poor integration of graft	9.30	4/43	3.5 yr	8 of 16
Fossum et al.[65]	2019	RCT/II	ACI, MACI	Conversion to arthroplasty and/or new resurfacing procedure, PROs (clinical deterioration in KOOS compared with baseline, VAS score, Lysholm score)	19.51	8/41	2 yr	19 of 24
Ebert et al.[66]	2021	RCT/II	MACI	Delamination or graft bed devoid of repair tissue; conversion to arthroplasty, confirmed by imaging; reoperation	8.11	3/37	5 yr	20 of 24

ACI, autologous chondrocyte implantation; ACL, anterior cruciate ligament; ACT, autologous chondrocyte transplantation; DFO, distal femoral osteotomy; EQ-VAS, EuroQol visual analog scale; HTO, high tibial osteotomy; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; LOE, level of evidence; MACI, matrix-induced autologous chondrocyte implantation; MACT, matrix-associated chondrocyte transplantation; MAT, meniscal allograft transplantation; MCL, medial collateral ligament; MCRS, modified Cincinatti rating scale; MINORS, Methodological Index for Non-randomized Studies; MOCART, magnetic resonance observation of cartilage repair tissue (scoring system); MST, marrow stimulating technique; OA, osteoarthritis; OAT, osteochondral autograft transfer; OCA, osteochondral allograft; PCL, posterior cruciate ligament; PRO, patient-reported outcome; RCT, randomized controlled trial; ROM, range of motion; SXS, symptoms; TAS, Tegner activity scale; TTO, tibial tubercle osteotomy; VAS, visual analog scale; VMO, vastus medialis oblique; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

met the inclusion criteria and were analyzed in this review[6-66] (Table 1). There were 8 Level II studies (8 of 61, 13.11%), 19 Level III studies (19 of 61, 31.11%), and 34 Level IV studies (34 of 61, 55.74%). The average Methodological Index for Non-randomized Studies score was 17.7 (range, 11-22) for comparative studies and 10.7 (range, 8-14) for noncomparative studies. There were numerous definitions of failure of knee chondral restoration surgery used in the current literature (Fig 2).

A total of 4,277 knees were included, with a total of 777 failed knee chondral restoration procedures. There were more male patients (62.35%) than female patients (37.65%). A plurality of studies included ACI as the singular knee chondral surgical technique (19 of 61, 31.14%). Additional knee chondral restoration techniques were included as follows: microfracture (2 of 61, 3.28%), OAT (2 of 61, 3.28%), osteochondral allograft transplantation (11 of 61, 18.03%), matrix-assisted autologous chondrocyte transplantation (10 of 61, 16.39%), autologous cartilage transplantation (2 of 61, 3.28%), and other surgical techniques (3 of 61, 4.92%).

Some studies included multiple surgical techniques, analyzing ACI and matrix-assisted autologous chondrocyte transplantation (2 of 61, 3.28%), ACI and microfracture (2 of 61, 3.28%), osteochondral allograft transplantation and OAT (1 of 61, 1.63%), ACI and OAT (1 of 61, 1.63%), matrix-assisted autologous chondrocyte transplantation and microfracture (3 of 61, 4.92%), OAT and microfracture (2 of 61, 3.28%), and ACI and osteochondral allograft transplantation (1 of 61, 1.63%) (Table 2). ACI plus microfracture was the combined surgical technique with the largest failure rate (39.46%). OAT had a failure rate of 38.06%, and ACI plus matrix-induced autologous chondrocyte implantation had a failure rate of 37.88%. OAT plus microfracture had a failure rate of 36.5% in this review. Isolated microfracture had a failure rate of 3.87% (Table 2). The weighted mean follow-up period was 6.59 years (range, 8 weeks to 26 years).

Subsequent Operations

Most publications included some type of reoperation in their definition of failure (54 of 61, 88.5%). Publications inclusive of this type of failure were any studies that indicated reoperation of the knee. Failure rates ranged from 3.22% to 75%. The most common definition of knee chondral restoration failure used was the need for any revision surgery (52 of 61 studies, 85.3%). Conversion to knee arthroplasty was another common definition (34 of 61, 55.7%) and was used more frequently than removal of graft or implant (14 of 61,

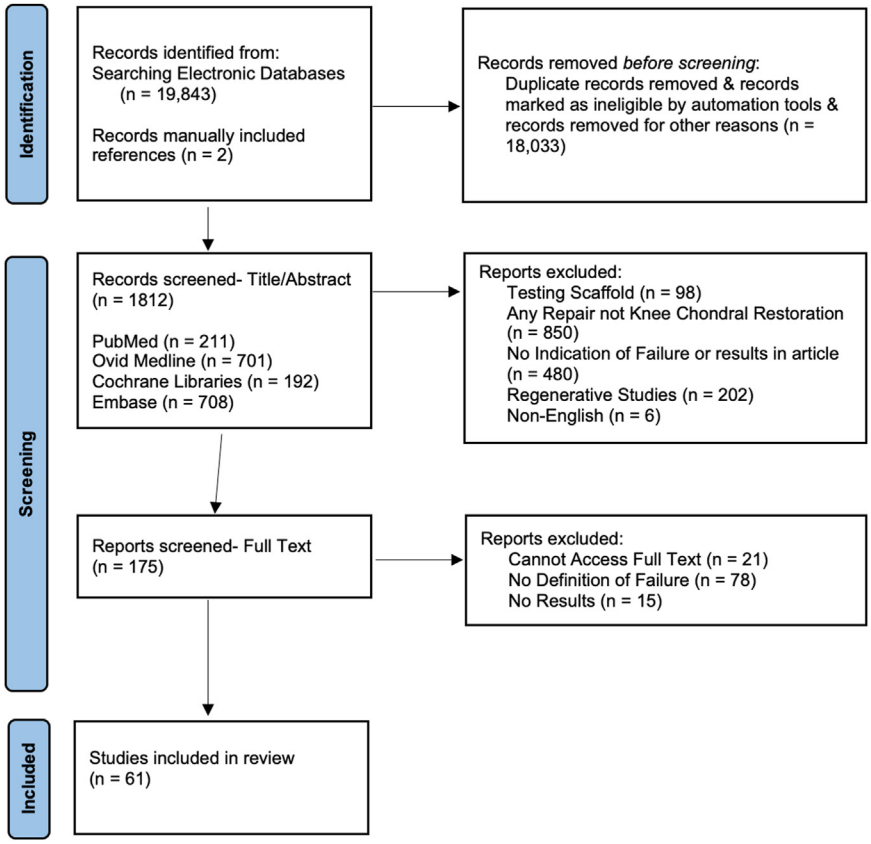

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart for inclusion of articles showing number of articles screened, included, and excluded at each stage. Each article was screened by 2 team members, and discrepancies were discussed and resolved by a third team member.

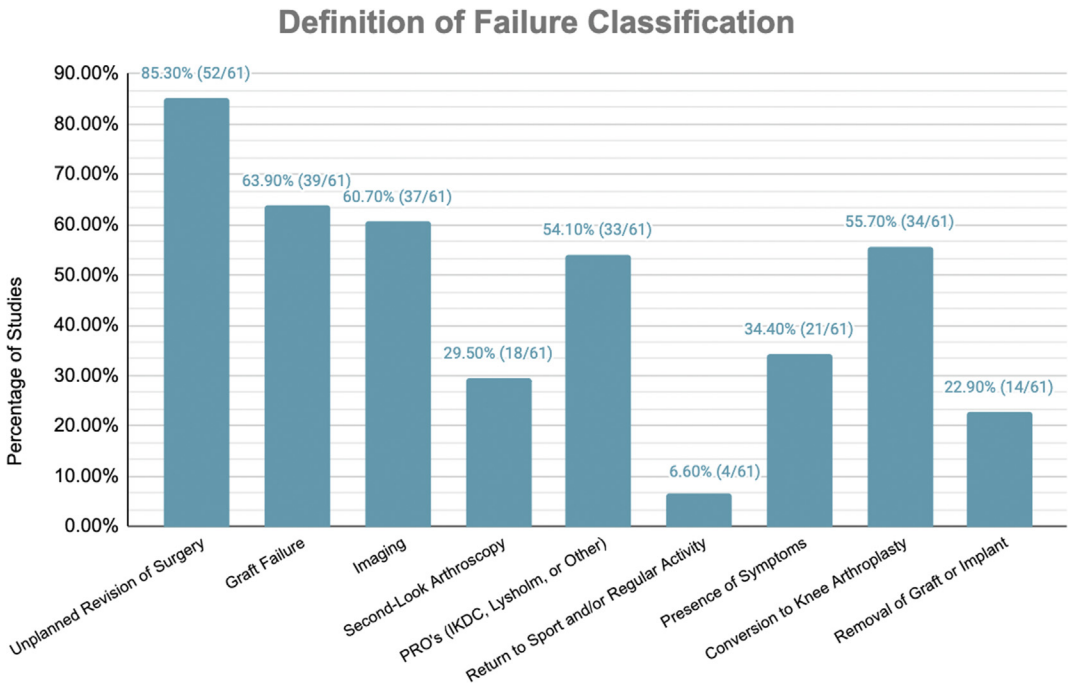

Fig 2. Definition of failure breakdown including percentage of each classification of failure definition in knee chondral restoration procedures. (IKDC, International Knee Documentation Committee; PRO, patient-reported outcome.)

22.9%). An additional definition in the included studies was other revisions (8 of 61, 13.1%).

Graft Failure

Publications that included graft failure in the definition of failure indicated that the knee tissue was inadequate and/or required treatment as a result of tissue deterioration or damage. Failure rates ranged from 2.10% to 47%. In some publications, graft failure was defined as delamination and/or graft inadequacy (39 of 61, 63.9%). Imaging (37 of 61, 60.7%) and second-look arthroscopy (18 of 61, 29.5%) were used to confirm graft failure. Imaging and second-look arthroscopy were used in combination in 13 studies (21.31%). Imaging alone was used to confirm failure in 24 studies (39.34%), whereas 5 studies (8.20%) used second-look arthroscopy solely to confirm failure.

Patient-Reported Outcomes

Multiple studies also used subjective PROs to define failed procedures, including but not limited to lack of significant improvement, failure to return to activity, or persistent pain using subjective measuring tools (33 of 61, 54.1%). Failure to return to sport and/or regular

Table 2. Breakdown of Knee Chondral Restoration Failure per Surgical Technique and Failure Rate

Knee Chondral Restoration Surgical Technique	No. of Studies	No. of Patients	Failure Rate, %	
			Mean	Range
ACI	19	1,106	23.08	4.50-47
Microfracture	2	119	3.87	2.10-5.63
OAT	2	111	38.06	25-51.11
OCA	11	894	17.61	3.75-42.62
MACT/MACI	10	695 (697 knees)	11.17	3.22-17
ACT	2	48	9.73	3.45-16
Other	3	69	16.22	14-18
ACI + MACI	2	57	37.88	19.51-33
ACI + OAT	1	359	10	7.6-15.19
ACI + OCA	1	43	9.3	9.30
ACI + microfracture	2	118	39.46	3.92-75
OAT + OCA	1	113	19	19
MACI + microfracture	3	135	23.16	2.17-59
OAT + microfracture	2	408	36.5	11-62

ACI, autologous chondrocyte implantation; ACT, autologous chondrocyte transplantation; MACI, matrix-induced autologous chondrocyte implantation; MACT, matrix-associated chondrocyte transplantation; OAT, osteochondral autograft transfer; OCA, osteochondral allograft.

activity was used to define failure in 4 studies (4 of 61, 6.56%).

The presence of postoperative symptoms was used to define failure in 21 articles (34.43%). Postoperative symptoms included pain, decreased limb function, inhibition of activity level, swelling, limited range of motion (ROM), and/or decreased overall quality of life. No clinical improvement was used to define failure in 13 articles (21.31%). Persistent pain was part of the definition in 5 articles (8.20%). Among these studies, the failure rates ranged from 3.45% to 59%.

The International Knee Documentation Committee questionnaire was the most used PRO measure, incorporated in 9 studies (14.75%). In 3 studies (4.92%), the absence of clinically significant improvement, specified as an increase in the International Knee Documentation Committee subjective score by 10 points or less compared with the baseline evaluation, was defined as failure.[8,14,19] The Lysholm score was used in 6 studies (9.84%), with failure most commonly defined as a score of less than 65 points.[24,25,27] Studies that used the Lysholm score to define failure indicated a range of failure rates from 13% to 62%. In addition, the Tegner activity scale was identified in 6 studies (9.84%); visual analog scale score, 6 studies (9.84%); Knee Injury and Osteoarthritis Outcome Score (KOOS), 5 studies (8.20%); modified Cincinnati knee rating system, 2 studies (3.28%); and Western Ontario and McMaster Universities Osteoarthritis Index, 1 study (1.64%). Among these studies, the failure rate ranged from 4.50% to 62%. Regarding the KOOS, failure was defined as any deterioration in the KOOS at follow-up compared with baseline.[65]

Multiple Definitions

Publications inclusive of multiple definitions indicated that there were 2 or more definitions that outlined failure postoperatively. All studies that used PROs as a concrete definition of failure paired other definitions of failure with this definition. In terms of binary modes of defining failure, subsequent procedures and PROs were identified as the most used combination; this combination was reported in 27 studies (27 of 61, 44.26%). Graft failure and delamination were paired with PROs in 1 study (1 of 61, 1.64%).

Failure Rates

The average failure rate of all included studies was approximately 20%. The 5 studies with the highest failure rates all included multiple outcomes to define knee chondral restoration failure.[22,25,27,42,51] Solheim et al.[25,27] produced 2 studies (2 of 61, 3.28%) that defined failure as a poor Lysholm score (<65 points) or reoperation on the knee (conversion to arthroplasty), and they indicated a failure rate of 51.11% with a mean follow-up period of 4 years and a failure rate of 62% with a mean follow-up period of 12 years. Thomas et al.[22] defined failure as the need for reoperation (conversion to arthroplasty) and no clinical improvement in PROs, including visual analog scale score, as well as inability to return to sport, continued symptoms, and persistent pain, and reported a failure rate of 42.62% with a mean follow-up period of 3.8 years. Tjörnstrand et al.[42] defined failure as any reoperation or progression to osteoarthritis confirmed by imaging and reported a failure rate of 75% with a mean follow-up period of 17 years. Zarkadis et al.[51] defined failure as reoperation (conversion to arthroplasty), inability to return to active military duty (based on PROs), and continued symptoms and indicated a failure rate of 45% with a mean follow-up period of 5 years. An average of 2 modes of failure were used in these studies, ranging between 1 mode and 3 modes of failure.[22,25,27,42,51] Reoperation was used as a definition of failure in all 5 studies, whereas PROs were used in 4 of these studies and return to activity was used in 2 of the top-5 studies.

The 5 studies with the lowest documented failure rates included 2 modes of failure on average. These studies ranged from 1 mode to 4 modes of failure. Anderson et al.[20] indicated a failure rate of 3.75% with a mean follow-up period of 3.6 years, with failure defined as reoperation (conversion to arthroplasty), removal of allograft, and graft inadequacy. Blanke et al.[28] defined failure as reoperation (conversion to arthroplasty), removal of tissue, tissue inadequacy, and persisting pain and symptoms based on PROs and reported a failure rate of 3.45% with a mean follow-up period of 2 years. Cole et al.[16] reported a failure rate of 2.1% with a mean follow-up period of 2 years and defined failure as graft delamination confirmed by imaging or arthroscopy. Hoburg et al.[10] reported a failure rate of 3.92% with a mean follow-up period of 3 years and defined failure as any follow-up reoperation. Zellner et al.[43] defined failure as inadequate integration confirmed by imaging or arthroscopy, as well as continued symptoms determined through PROs (limited ROM), and indicated a failure rate of 2.17% with a median follow-up period of 2 years. PROs were included in only 2 of these studies.

Discussion

The most important finding of this systematic review was the consistency of revision surgery as the main component of failure across most included studies (52 of 61, 85.3%). Graft failure, defined as delamination and/or graft inadequacy, was the second most common definition of failure identified in this review (39 of 61, 63.9%). PROs were also highlighted as a common definition of failure in multiple studies (33 of 61, 54.1%). Subsequent procedures and PROs were identified to be used in conjunction as binary modes of

failure in 27 studies (44.26%). The studies that showed the top-5 highest failure rates, that is, 51.11%, 62%, 42.62%, 75%, and 45%, included multiple definitions of failure, and reoperation was used as a definition of failure in all of these studies. The mean follow-up time for each study was 4 years, 12 years, 3.8 years, 17 years, and 5 years, respectively.[22,25,27,42,51] Of the 5 studies with the lowest failure rates, that is, 3.92%, 2.1%, 3.75%, 3.45%, and 2.17%, 2 studies used only 1 outcome to determine failure. The follow-up time for each of these studies was a mean of 3.6 years, mean of 2 years, mean of 2 years, mean of 3 years, and median of 2 years, respectively.[10,16,20,28,43]

Conversion to arthroplasty was described as the primary definition of failure in 34 studies (55.74%). Knee arthroplasty is a more indicative procedure for failure because it seeks to relieve issues that cannot be resolved via arthroscopic or nonoperative means. However, knee arthroplasty is typically pursued in older patient populations. As such, conversion to arthroplasty is an unrealistic endpoint in young and/or highly active patients and thus undervalues the true extent of treatment failure if used solely.[67] Furthermore, there are patients who elect for nonoperative treatment after suboptimal outcomes of primary cartilage surgery.[68] These patients may have an unacceptable body mass index, diabetes control, and/or tobacco use that precludes an arthroplasty procedure. Moreover, others may not pursue arthroplasty because of financial reasons. With this in mind, even though conversion to arthroplasty is an acceptable definition of failure, it cannot be used solely because it will underestimate the degree of patients with suboptimal results.

The second most common definition of failure was graft failure, defined as delamination and/or graft inadequacy. Examples of graft failure include visible graft collapse due to inadequate integration and tissue infill discrepancies.[39,41] Martinčič et al.[21] defined graft failure as revision cartilage repair, arthroplasty, or low clinical outcome together with radiologic or arthroscopic evidence of failure. In addition, several articles included graft failure and revision surgery to expand the criteria for knee chondral restoration failure. Broadening the failure definition more accurately reflects the reality in which some patients are not offered or do not pursue revision surgery despite having documented graft failure.[31] It is important to note that advanced imaging and second-look arthroscopy are great tools for confirming failure. No included studies specified that imaging alone defined failure; rather, it was used to confirm failure determined by other means such as functional outcomes. Second-look arthroscopy is commonly used for diagnostic and therapeutic purposes if patients have continued symptoms postoperatively.

PROs are also an important factor in defining failure. In this review, 54.1% of studies highlighted PROs in their definition of failure (n = 33). The presence of continued symptoms was the most used indication of failure, occurring in 21 studies (34.42%). Postoperative symptoms included pain, decreased limb function, inhibition of activity level, swelling, limited ROM, and/or decreased overall quality of life. Evaluating self-reported outcomes as a determinant between success and failure is essential and provides useful support for the complex shared decision-making process between the surgeon and the patient.[69] Lack of significant improvement and/or presence of persistent pain is a critical factor that a surgeon needs to consider when evaluating a patient and determining knee chondral restoration failure. It is important to note that personal interpretations postoperatively may be more important than objective PROs. For instance, in the study by Ogura et al.,[59] 4 patients rated their knee as better postoperatively and they were also satisfied with the surgical procedure even though they objectively had failure based on a lack of clinical improvement according to the modified Cincinnati score. With this in mind, objective PROs are vital to postsurgical assessment; however, a surgeon must not overlook the patient's subjective self-assessment as well.

Although PROs allow surgeons to effectively evaluate patients postoperatively, one should keep in mind the heterogeneity in scoring systems and patient populations that could influence failure rates. For example, a recent study noted that "older participants showed higher pain thresholds than younger," and as a result, despite similar pathology, the reported outcomes are expected to be different.[70] The abundance of available scoring systems, along with cutoff parameters, further complicates the understanding of failure after knee chondral restoration surgery. We recommend using standardized PRO measures such as the minimal clinically important difference, patient acceptable symptomatic state, and substantial clinical benefit that are specific to the patient cohort to minimize this heterogeneity.

One useful description of failure is the inability to return to sport. Younger, more active patients will seek surgical intervention to relieve pain, address athletic injuries, and enhance performance. Zaffagnini et al.[56] found that 64.5% of patients were able to return to a competitive level after chondral restoration procedures whereas 58.1% of the same patients performed at the same preinjury level. Although these authors did not use return to sport to determine failure, their study discussed how the level of activity is of much greater importance to athletes than any score or functional parameter. The ability to return to the same level of sport activity or functional ability must be considered a main outcome in athletic or military personnel. If the preinjury level of function is not achieved, the surgical procedure should be considered a failure. However, a

competitive athlete's goal may be vastly different from that of a middle-aged patient who hopes to perform activities of daily living and ambulate without pain.

The need to define the term "failure" for knee chondral restoration procedures is essential because it will offer surgeons a standardized measure to counsel patients before surgery and assess patients after surgery. One primary objective in knee chondral restorative procedures is to conserve patients' native tissue. A standard definition of failure across all procedures facilitates comparison between their outcomes. Currently, the varied definitions of knee chondral restoration failure among authors may lead to an inaccurate representation of facts when discussing goals of care with patients or when providers are attempting to estimate the success of a procedure.[31] Although this may be challenging given the heterogeneity in pathology, treatment, and complexity of the injury, a standardized definition of failure is essential. We recommend including binary outcomes such as unplanned surgical procedures and PROs with standardized measures of minimal clinically important difference, patient acceptable symptomatic state, and substantial clinical benefit, along with the ability to return to normal function, as the main factors to define failure. Furthermore, the ability to compete at a high level in athletes or return to duty in military personnel should be implemented. Advanced imaging and/or second-look arthroscopy is a helpful tool that may aid in diagnosing and confirming chondral failures. It is essential for each surgeon to cater factors of failure to his or her specific cohort to establish proper expectations after knee cartilage surgery.

Although our recommendations will inherently increase "failure rates" among patients, it is important to use this knowledge to properly counsel patients about realistic outcomes after knee chondral restoration surgery. Using our recommendation for defining failure will equip surgeons with a better understanding of the risks, benefits, and consequences of knee chondral restoration procedures, allowing for better education and expectations for patients.

Limitations

The limitations of this study largely reflect the heterogeneity of the pathology discussed. There are many indications, surgical procedures, and techniques available to address chondral pathology. This reality, combined with the heterogeneity of patient populations, presenting symptoms, PROs, activity levels and comorbidities, makes it difficult to standardize the definition of failure to each patient. Another limitation in this study was the inclusion of studies with patients of differing lengths of postoperative follow-up. Inconsistent follow-up periods may result in variations in failure rates.

Conclusions

A variety of definitions of failure are used to evaluate knee chondral restorative surgery outcomes in the orthopaedic literature. Any unplanned revision surgery and graft failure, defined as delamination and/or graft inadequacy, were the most common criteria defining knee chondral restoration failure. Patients' functionality and quality of life, determined by PROs, were also used to define knee chondral restoration failure in multiple studies. Higher rates of failure were observed after knee chondral restorative procedures when using multiple definitions of failure that were more inclusive. To account for heterogeneity in definitions, procedures, and patient circumstances, we recommend using multiple outcomes, including unplanned surgical procedures, PROs, and the ability to return to the desired level of function, as factors to define failure.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: B.G.V. reports a consulting or advisory relationship with Artelon and Stryker and owns equity or stocks in Altior, Carbon 22, and Spinal Simplicity. All other authors (L.F., M.T., E.G., A.T., E.H., P.S., C.D.B., R.L., T.M., J.W.) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: Study of 25,124 knee arthroscopies. *Knee* 2007;14:177-182.
2. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy* 2002;18:730-734.
3. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: A review of 31,516 knee arthroscopies. *Arthroscopy* 1997;13:456-460.
4. Migliorini F, Eschweiler J, Schenker H, Baroncini A, Tingart M, Maffulli N. Surgical management of focal chondral defects of the knee: A Bayesian network meta-analysis. *J Orthop Surg Res* 2021;16:543.
5. Mundi R, Bedi A, Chow L, et al. Cartilage restoration of the knee: A systematic review and meta-analysis of level 1 studies. *Am J Sports Med* 2016;44:1888-1895.
6. Barbieri Mestriner A, Ackermann J, Morlin Ambra LF, Franciozi CE, Faloppa F, Gomoll AH. Trochlear dysplasia does not affect the outcomes of patellofemoral autologous chondrocyte implantation. *Arthroscopy* 2020;36:3019-3027.
7. Barié A, Kruck P, Sorbi R, et al. Prospective long-term follow-up of autologous chondrocyte implantation with periosteum versus matrix-associated autologous chondrocyte implantation: A randomized clinical trial. *Am J Sports Med* 2020;48:2230-2241.

8. Di Martino A, Silva S, Andriolo L, et al. Osteochondral autograft transplantation versus autologous bone-cartilage paste grafting for the treatment of knee osteochondritis dissecans. *Int Orthop* 2021;45:453-461.
9. Gomoll AH, Ambra LF, Phan A, Mastrocola M, Shah N. Cell-seeded autologous chondrocyte implantation: A simplified implantation technique that maintains high clinical outcomes. *Am J Sports Med* 2017;45:1028-1036.
10. Hoburg A, Niemeyer P, Laute V, et al. Matrix-associated autologous chondrocyte implantation with spheroid technology is superior to arthroscopic microfracture at 36 months regarding activities of daily living and sporting activities after treatment. *Cartilage* 2021;13:437S-448S (suppl).
11. Riff AJ, Huddleston HP, Cole BJ, Yanke AB. Autologous chondrocyte implantation and osteochondral allograft transplantation render comparable outcomes in the setting of failed marrow stimulation. *Am J Sports Med* 2020;48:861-870.
12. Pike AN, Bryant T, Ogura T, Minas T. Intermediate- to long-term results of combined anterior cruciate ligament reconstruction and autologous chondrocyte implantation. *Orthop J Sports Med* 2017;5:2325967117693591.
13. Teo AQA, Wong KL, Shen L, et al. Equivalent 10-year outcomes after implantation of autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation for chondral defects of the knee. *Am J Sports Med* 2019;47:2881-2887.
14. Roffi A, Andriolo L, Di Martino A, et al. Long-term results of matrix-assisted autologous chondrocyte transplantation combined with autologous bone grafting for the treatment of juvenile osteochondritis dissecans. *J Pediatr Orthop* 2020;40:e115-e121.
15. von Keudell A, Han R, Bryant T, Minas T. Autologous chondrocyte implantation to isolated patella cartilage defects. *Cartilage* 2017;8:146-154.
16. Cole BJ, Haunschild ED, Carter T, et al. Clinically significant outcomes following the treatment of focal cartilage defects of the knee with microfracture augmentation using cartilage allograft extracellular matrix: A multicenter prospective study. *Arthroscopy* 2021;37:1512-1521.
17. Johnson CC, Johnson DJ, Garcia GH, et al. High short-term failure rate associated with decellularized osteochondral allograft for treatment of knee cartilage lesions. *Arthroscopy* 2017;33:2219-2227.
18. Ibarra C, Villalobos E, Madrazo-Ibarra A, et al. Arthroscopic matrix-assisted autologous chondrocyte transplantation versus microfracture: A 6-year follow-up of a prospective randomized trial. *Am J Sports Med* 2021;49:2165-2176.
19. Cinats D, Miller S, Abusara Z, et al. Evolution of a novel tissue preservation protocol to optimize osteochondral transplantation outcomes. *Cartilage* 2021;12:31-41.
20. Anderson DE, Robinson KS, Wiedrick J, Crawford DC. Efficacy of fresh osteochondral allograft transplantation in the knee for adults 40 years and older. *Orthop J Sports Med* 2018;6:2325967118805441.
21. Martinčič D, Mekač J, Drobnič M. Survival rates of various autologous chondrocyte grafts and concomitant procedures. A prospective single-center study over 18 years. *Cell Transplant* 2019;28:1439-1444.
22. Thomas D, Shaw KA, Waterman BR. Outcomes after fresh osteochondral allograft transplantation for medium to large chondral defects of the knee. *Orthop J Sports Med* 2019;7:2325967119832299.
23. Wang D, Rebolledo BJ, Dare DM, et al. Osteochondral allograft transplantation of the knee in patients with an elevated body mass index. *Cartilage* 2019;10:214-221.
24. Wang D, Marom N, Coxe FR, et al. Preoperative grades of osteoarthritis and meniscus volume correlate with clinical outcomes of osteochondral graft treatment for cartilage defects in the knee. *Cartilage* 2021;12:344-353.
25. Solheim E, Hegna J, Inderhaug E. Long-term survival after microfracture and mosaicplasty for knee articular cartilage repair: A comparative study between two treatments cohorts. *Cartilage* 2020;11:71-76.
26. Solheim E, Hegna J, Inderhaug E. Early determinants of long-term clinical outcome after cartilage repair surgery in the knee. *J Orthop* 2018;15:222-225.
27. Solheim E, Hegna J, Inderhaug E. Clinical outcome after mosaicplasty of knee articular cartilage defects of patellofemoral joint versus tibiofemoral joint. *J Orthop* 2019;18:36-40.
28. Blanke F, Oehler N, Haenle M, Lenz R, Vogt S, Tischer T. All-arthroscopic hydrogel-based autologous chondrocyte transplantation in the knee joint: Good clinical and magnetic resonance imaging outcome after 24 months. *Arthroscopy* 2021;37:1892-1899.
29. Balazs GC, Wang D, Burge AJ, Sinatro AL, Wong AC, Williams RJ. Return to play among elite basketball players after osteochondral allograft transplantation of full-thickness cartilage lesions. *Orthop J Sports Med* 2018;6:2325967118786941.
30. Merkely G, Ogura T, Ackermann J, Barbieri Mestriner A, Gomoll AH. Clinical outcomes after revision of autologous chondrocyte implantation to osteochondral allograft transplantation for large chondral defects: A comparative matched-group analysis. *Cartilage* 2021;12:155-161.
31. Ackermann J, Barbieri Mestriner A, Arango D, Ogura T, Gomoll AH. Validation of the Oswestry Risk of Knee Arthroplasty Index (ORKA-1) for patients undergoing autologous chondrocyte implantation. *Cartilage* 2020;11:405-411.
32. Beck JJ, Sugimoto D, Micheli L. Sustained results in long-term follow-up of autologous chondrocyte implantation (ACI) for distal femur juvenile osteochondritis dissecans (JOCD). *Adv Orthop* 2018;2018:7912975.
33. Kim JK, Vaidya R, Lee SK, et al. Clinical and radiological changes after microfracture of knee chondral lesions in middle-aged Asian patients. *Clin Orthop Surg* 2019;11:282-290.
34. Carey JL, Shea KG, Lindahl A, Vasiliadis HS, Lindahl C, Peterson L. Autologous chondrocyte implantation as treatment for unsalvageable osteochondritis dissecans: 10- to 25-year follow-up. *Am J Sports Med* 2020;48:1134-1140.
35. Stannard JP, Cook JL. Prospective assessment of outcomes after primary unipolar, multisurface, and bipolar osteochondral allograft transplantations in the knee: A comparison of 2 preservation methods. *Am J Sports Med* 2020;48:1356-1364.
36. Ebert JR, Schneider A, Fallon M, Wood DJ, Janes GC. A comparison of 2-year outcomes in patients undergoing

tibiofemoral or patellofemoral matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2017;45:3243-3253.
37. Ebert JR, Fallon M, Wood DJ, Janes GC. A prospective clinical and radiological evaluation at 5 years after arthroscopic matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2017;45:59-69.
38. Ebert JR, Fallon M, Wood DJ, Janes GC. Long-term prospective clinical and magnetic resonance imaging-based evaluation of matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2021;49:579-587.
39. Ebert JR, Fallon M, Janes G, Wood D. Minimum 10 year clinical and radiological outcomes of a randomized controlled trial evaluating accelerated weight bearing after matrix-induced autologous chondrocyte implantation. *Orthop J Sports Med* 2019;7(suppl 5):2325967119S00260.
40. Ebert JR, Fallon M, Ackland TR, Janes GC, Wood DJ. Minimum 10-year clinical and radiological outcomes of a randomized controlled trial evaluating 2 different approaches to full weightbearing after matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2020;48:133-142.
41. Ebert JR, Edwards PK, Fallon M, Ackland TR, Janes GC, Wood DJ. Two-year outcomes of a randomized trial investigating a 6-week return to full weightbearing after matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2017;45:838-848.
42. Tjörnstrand J, Neuman P, Lundin B, Svensson J, Dahlberg LE, Tiderius CJ. Poor outcome after a surgically treated chondral injury on the medial femoral condyle: Early evaluation with dGEMRIC and 17-year radiographic and clinical follow-up in 16 knees. *Acta Orthop* 2018;89:431-436.
43. Zellner J, Grechenig S, Pfeifer CG, et al. Clinical and radiological regeneration of large and deep osteochondral defects of the knee by bone augmentation combined with matrix-guided autologous chondrocyte transplantation. *Am J Sports Med* 2017;45:3069-3080.
44. Schüttler KF, Götschenberg A, Klasan A, et al. Cell-free cartilage repair in large defects of the knee: Increased failure rate 5 years after implantation of a collagen type I scaffold. *Arch Orthop Trauma Surg* 2019;139:99-106.
45. Yoon KH, Kang SG, Kwon YB, Kim EJ, Kim SG. Clinical outcomes and survival rate of autologous chondrocyte implantation with and without concomitant meniscus allograft transplantation: 10- to 15-year follow-up study. *Arch Orthop Trauma Surg* 2019;139:1117-1123.
46. Andriolo L, Di Martino A, Altamura SA, et al. Matrix-assisted chondrocyte transplantation with bone grafting for knee osteochondritis dissecans: Stable results at 12 years. *Knee Surg Sports Traumatol Arthrosc* 2021;29:1830-1840.
47. Andriolo L, Reale D, Di Martino A, et al. Long-term results of arthroscopic matrix-assisted autologous chondrocyte transplantation: A prospective follow-up at 15 years. *Am J Sports Med* 2020;48:2994-3001.
48. Andriolo L, Reale D, Di Martino A, et al. High rate of failure after matrix-assisted autologous chondrocyte transplantation in osteoarthritic knees at 15 years of follow-up. *Am J Sports Med* 2019;47:2116-2122.
49. Tírico LEP, McCauley JC, Pulido PA, Bugbee WD. Osteochondral allograft transplantation of the femoral condyle utilizing a thin plug graft technique. *Am J Sports Med* 2019;47:1613-1620.
50. Berruto M, Ferrua P, Pasqualotto S, et al. Long-term follow-up evaluation of autologous chondrocyte implantation for symptomatic cartilage lesions of the knee: A single-centre prospective study. *Injury* 2017;48:2230-2234.
51. Zarkadis NJ, Kusnezov NA, Garcia EJ, Pallis MP, Waterman BR. Return to preoperative function after autologous cartilage implantation of the knee in active military servicemembers. *Orthop J Sports Med* 2017;5:2325967117706057.
52. Müller PE, Gallik D, Hammerschmid F, et al. Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results. *Knee Surg Sports Traumatol Arthrosc* 2020;28:470-477.
53. Frank RM, Lee S, Levy D, et al. Osteochondral allograft transplantation of the knee: Analysis of failures at 5 years. *Am J Sports Med* 2017;45:864-874.
54. Siebold R, Suezer F, Schmitt B, Trattnig S, Essig M. Good clinical and MRI outcome after arthroscopic autologous chondrocyte implantation for cartilage repair in the knee. *Knee Surg Sports Traumatol Arthrosc* 2018;26:831-839.
55. León SA, Mei XY, Safir OA, Gross AE, Kuzyk PR. Long-term results of fresh osteochondral allografts and realignment osteotomy for cartilage repair in the knee. *Bone Joint J* 2019;101-B:46-52 (suppl A).
56. Zaffagnini S, Vannini F, Di Martino A, et al. Low rate of return to pre-injury sport level in athletes after cartilage surgery: A 10-year follow-up study. *Knee Surg Sports Traumatol Arthrosc* 2019;27:2502-2510.
57. Saris TFF, de Windt TS, Kester EC, Vonk LA, Custers RJH, Saris DBF. Five-year outcome of 1-stage cell-based cartilage repair using recycled autologous chondrons and allogenic mesenchymal stromal cells: A first-in-human clinical trial. *Am J Sports Med* 2021;49:941-947.
58. Minas T, Ogura T, Headrick J, Bryant T. Autologous chondrocyte implantation "sandwich" technique compared with autologous bone grafting for deep osteochondral lesions in the knee. *Am J Sports Med* 2018;46:322-332.
59. Ogura T, Mosier BA, Bryant T, Minas T. A 20-year follow-up after first-generation autologous chondrocyte implantation. *Am J Sports Med* 2017;45:2751-2761.
60. Ogura T, Sakai H, Asai S, et al. Clinical and radiographic outcomes after fixation of chondral fragments of the knee in 6 adolescents using autologous bone pegs. *Orthop J Sports Med* 2020;8:2325967120963050.
61. Ogura T, Bryant T, Minas T. Long-term outcomes of autologous chondrocyte implantation in adolescent patients. *Am J Sports Med* 2017;45:1066-1074.
62. Ogura T, Bryant T, Mosier BA, Minas T. Autologous chondrocyte implantation for bipolar chondral lesions in the tibiofemoral compartment. *Am J Sports Med* 2018;46:1371-1381.
63. Ogura T, Bryant T, Merkely G, Mosier BA, Minas T. Survival analysis of revision autologous chondrocyte implantation for failed ACI. *Am J Sports Med* 2019;47:3212-3220.
64. Wang T, Wang DX, Burge AJ, et al. Clinical and MRI outcomes of fresh osteochondral allograft transplantation

after failed cartilage repair surgery in the knee. *J Bone Joint Surg Am* 2018;100:1949-1959.
65. Fossum V, Hansen AK, Wilsgaard T, Knutsen G. Collagen-covered autologous chondrocyte implantation versus autologous matrix-induced chondrogenesis: A randomized trial comparing 2 methods for repair of cartilage defects of the knee. *Orthop J Sports Med* 2019;7:2325967119868212.
66. Ebert JR, Fallon M, Wood DJ, Janes GC. An accelerated 6-week return to full weight bearing after matrix-induced autologous chondrocyte implantation results in good clinical outcomes to 5 years post-surgery. *Knee Surg Sports Traumatol Arthrosc* 2021;29:3825-3833.
67. Bayliss LE, Culliford D, Monk AP, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. *Lancet* 2017;389:1424-1430.
68. Krych AJ, Hevesi M, Desai VS, Camp CL, Stuart MJ, Saris DBF. Learning from failure in cartilage repair surgery: An analysis of the mode of failure of primary procedures in consecutive cases at a tertiary referral center. *Orthop J Sports Med* 2018;6:2325967118773041.
69. Price AJ, Kang S, Cook JA, et al. The use of patient-reported outcome measures to guide referral for hip and knee arthroplasty. *Bone Joint J* 2020;102-B:941-949.
70. González-Roldán AM, Terrasa JL, Sitges C, van der Meulen M, Anton F, Montoya P. Age-related changes in pain perception are associated with altered functional connectivity during resting state. *Front Aging Neurosci* 2020;12:116.