

TABLE E-1 Delphi List*

1. Treatment allocation
(a) Was a method of randomization performed?
(b) Was the treatment allocation concealed?
2. Were the groups similar at baseline regarding the most important prognostic indicators?
3. Were the eligibility criteria specified?
4. Was the outcome assessor blinded?
5. Was the care provider blinded?
6. Was the patient blinded?
7. Were point estimates and measures of variability presented for the primary outcome measures?
8. Did the analysis include an intention-to-treat analysis?

*The quality score is the sum of all questions, with 1 point given for “yes,” 1 point deducted for “no,” and 0 points for “don’t know.”

TABLE E-2 Modified Coleman Methodology Score*

	Score
Inclusion criteria	
Not described	0
Described without percentages given	3
Enrollment rate <80%	6
Enrollment rate >80%	9
Power	
Not reported	0
>80%, methods not described	3
>80%, methods described	6
Alpha error (α)	
Not reported	0
<0.05	3
<0.01	6
Sample size	
Not stated or <20	0
20 to 40	3
41 to 60	6
>60	9
Randomization	
Not randomized	0
Modified/partial	
Not blinded	2
Blinded	4
Complete	
Not blinded	6
Blinded	8
Follow-up	
Short-term (<6 months)	
Patient retention <80%	0
Patient retention 80% to 90%	2
Patient retention >90%	4
Medium-term (6 to 24 months)	
Patient retention <80%	2

Patient retention 80% to 90%	4
Patient retention >90%	6
Long-term (>24 months)	
Patient retention <80%	4
Patient retention 80% to 90%	6
Patient retention >90%	8
Patient analysis	
Incomplete	0
Complete	3
Complete and intention-to-treat based	6
Blinding	
None	0
Single	2
Double	4
Triple	6
Similarity in treatment	
No	0
Similar co-interventions	3
No co-interventions	6
Treatment description	
None	0
Fair	3
Adequate	6
Group comparability	
Not comparable	0
Partially comparable	3
Comparable	6
Outcome assessment	
Written assessment by patient with assistance	0
Written assessment by patient without assistance	2
Independent investigator	4
Recruited patients	6
Description of rehabilitation protocol	

Not reported	0
Not adequately described	2
Well described	4
Clinical effect measurement	
Effect size	
Not reported	0
<50%	2
50% to 75%	4
>75%	6
or relative risk reduction	
Not reported	0
<25%	3
>25%	6
or absolute risk reduction	
Not reported	0
<10%	3
>10%	6
Number of patients to treat	
Not reported	0
Reported	4

*A scaled score of 0 to 100 was graded as excellent (85 to 100), good (70 to 84), fair (55 to 69), or poor (<55).

TABLE E-3 Delphi List Quality Scores and Modified Coleman Methodology Scores

Study	Delphi List Quality Score	Modified Coleman Methodology Score
Basad ¹⁷ , 2010	2	52
Saris ⁵ , 2009	1	58
Kon ⁸ , 2009	−1	47
Zeifang ¹⁸ , 2010	3	61
Saris ³⁸ , 2008	3	64
Ferruzzi ⁴¹ , 2008	−3	50
Knutsen ⁷ , 2007	1	62
Gooding ⁴³ , 2006	1	58
Dozin ⁴⁰ , 2005	−1	56
Bartlett ³⁹ , 2005	−3	51
Knutsen ³⁷ , 2004	3	64
Basad ⁴⁴ , 2004	−5	36
Horas ⁴² , 2003	−1	44

TABLE E-4 Study Demographic Data and Patient Characteristics: Comparative Studies of ACI vs. Microfracture or OATS (Nine Studies, 639 Patients)*

	Evidence Level	Interventions†	Minimum Follow-up (mo)	Age‡ (yr)	Duration of Symptoms‡ (mo)	Percentage of Subjects with Previous Surgery	Defect Size‡ (cm ²)	Defect Location (%)	Percentage of Subjects with Single Defect
ACI vs. Mfx									
Basad ¹⁷ , 2010	I	Open ACI 2nd gen (40); Mfx (20)	24	34.2	27	NR	NR (range, 4 to 10)	MFC/LFC 75; Pat/Trochlea 25	100
Saris ⁵ , 2009	I	Open P-CCI (57); Mfx (61)	36	33.9	21.2	82	2.5	FC 100	97
Kon ⁸ , 2009	II	AKS ACI 2nd gen (40); Mfx (40)	60	29.8	NR	35	2.4	MFC 68; LFC 28; Trochlea 4	NR
Saris ³⁸ , 2008	I	Open P-CCI (57); Mfx (61)	18	33.9	21.2	82	2.5	FC 100	97
Knutsen ⁷ , 2007	I	Open PACI (40); Mfx (40)	60	32.2	36	95	4.8	MFC 89; LFC 11	100
Knutsen ³⁷ , 2004	I	Open PACI (40); Mfx (40)	24	32.2	36	95	4.8	MFC 89; LFC 11	100
Basad ⁴⁴ , 2004	II	Open ACI 2nd gen (10); Mfx (9)	12	33	NR	NR	4	NR	NR
ACI vs. OATS									
Dozin ⁴⁰ , 2005	II	Open PACI (22); OATS (22)	36	28.7	NR	0	1.9	MFC 59; LFC 11; Pat 30	99
Horas ⁴² , 2003	II	Open PACI (20); OATS (20)	24	33.4	NR	28	3.8	MFC 83; LFC 17	98

*ACI = autologous chondrocyte implantation; OATS = osteochondral autograft transfer; Mfx = microfracture; NR = not reported; MFC = medial femoral condyle; LFC = lateral femoral condyle; Pat = patella; P-CCI = periosteum cover, characterized chondrocyte implantation; FC = femoral condyle; AKS ACI = arthroscopic autologous chondrocyte implantation; PACI = periosteum cover, autologous chondrocyte implantation. †The number of subjects is given in parentheses. ‡The values are given as the mean, unless otherwise specified.

TABLE E-5 Study Demographic Data and Patient Characteristics: Intergenerational Comparative ACI Studies (Four Studies, 278 Patients)*

	Evidence Level	Interventions†	Minimum Follow-up (mo)	Age‡ (yr)	Duration of Symptoms‡ (mo)	Percentage of Subjects with Preoperative Surgery	Defect Size‡ (cm ²)	Defect Location (%)	Percentage of Subjects with Single Defect
Zeifang ¹⁸ , 2010	I	Open PACI (10); Open ACI 2nd gen (11)	24	29.3	28.5	100	4.1	MFC 86; LFC 14	100
Ferruzzi ⁴¹ , 2008	II	Open PACI (48); AKS ACI 2nd gen (50)	60	31.5	NR	NR	6.2	MFC 80; LFC 20	NR
Gooding ⁴³ , 2006	II	Open PACI (33); Open CACI (35)	24	30.5	85.1	100	4.5	MFC 38; LFC 16; Pat 40; Trochlea 6	100
Bartlett ³⁹ , 2005	II	Open CACI (44); Open ACI 2nd gen (47)	12	33.6	103	100	6.1	MFC 55; LFC 12; Pat 40; Trochlea 16	89

*ACI = autologous chondrocyte implantation; PACI = periosteum cover, autologous chondrocyte implantation; MFC = medial femoral condyle; AKS ACI = arthroscopic autologous chondrocyte implantation; NR = not reported; LFC = lateral femoral condyle; CACI = Type I/III collagen-membrane autologous chondrocyte implantation; Pat = patella. †The number of subjects is given in parentheses. ‡The values are given as the mean.

TABLE E-6 Study Outcomes Analysis: Comparative Studies of ACI vs. Microfracture or OATS (Nine Studies)*

	Randomization Method	Independent Clinical Examiner	Outcome Measures	Effect Size (Standard Error)	95% Confidence Interval (Lower)	95% Confidence Interval (Upper)	Summaries
ACI vs. Mfx							
Basad ¹⁷ , 2010	Computerized randomization	Not reported	Lysholm 1 yr	0.66 (0.31)†	0.05	1.25	Lysholm: ACI 52, Mfx 55 (preop.); ACI 95, Mfx 81 (1 yr); ACI 92, Mfx 69 (2 yr). Tegner: ACI 2, Mfx 2 (preop.); ACI 4, Mfx 3 (2 yr). ICRS patient and surgeon scores significantly better for ACI than Mfx
			Lysholm 2 yr	1.42 (0.34)†	0.72	2.07	
			Tegner 2 yr	0.72 (0.30)†	0.12	1.30	
			ICRS 2 yr	0.76 (0.37)†	0.02	1.48	
Saris ⁵ , 2009	IVRS minimization	No	KOOS (overall) 3 yr	1.52 (0.25)†	1.03	2.01	KOOS: CCI 78, Mfx 75 (3 yr); CCI 56, Mfx 56 (preop.). Significantly improved subdomains pain, QoL. Mfx outcome plateau at 18 mo.
Kon ⁸ , 2009	Not randomized	No	IKDC subjective 5 yr	0.76 (0.23) †	0.31	1.21	IKDC objective: ACI 90% normal/near normal, Mfx 75% (5 yr); ACI 15% normal/near normal, Mfx 2.5% (preop.). IKDC subjective: ACI 80, Mfx 70 (5 yr); ACI 41, Mfx 41 (preop). RTS similar at 2 yr; remained stable at 5 yr in ACI, declined in Mfx
Saris ³⁸ , 2008	IVRS minimization	Yes	KOOS (overall) 1.5 yr	0.23 (0.19)	-0.14	0.61	KOOS: CCI 75, Mfx 75 (1.5 yr); CCI 56, Mfx 59 (preop.). Significantly better structural repair and histology after ACI.
			Histomorphologic score 1 yr	0.46 (0.20)†	0.08	0.85	
			Histology score 1 yr	0.39 (0.19)†	0.01	0.77	
Knutsen ⁷ , 2007	Sealed envelopes	No	Lysholm 5 yr	-0.25 (0.20)	-0.64	0.15	Lysholm: ACI 75, Mfx 77 (5 yr). SF-36: ACI 48, Mfx 46 (5 yr). Better outcomes: <30 yr old. No correlation between histology and clinical outcome
			SF-36 (physical component) 5 yr	-0.40 (0.20)	-0.79	0.01	

Knutsen ³⁷ , 2004	Sealed envelopes	Yes	Lysholm 1 yr	−0.39 (0.23)	−0.83	0.06	Lysholm: ACI 71, Mfx 75 (2 yr); ACI 57, Mfx 55 (preop.) SF-36 (physical component): ACI 42, Mfx 46 (2 yr); ACI 41, Mfx 37 (preop.). Better outcomes: <30 yr old, Tegner >4. Mfx better outcome if defect < 4 cm ²
			Lysholm 2 yr	−0.28 (0.22)	−0.71	0.17	
			SF-36 (physical component) 2 yr	−0.65 (0.23)‡	−1.09	−0.19	
Basad ⁴⁴ , 2004	Randomization method not reported	No	Lysholm 1 yr	0.92 (0.48)	−0.06	1.82	Lysholm: ACI 95, Mfx 73 (1 yr); ACI 47, Mfx 58 (preop.). IKDC objective: MACI 90% normal/near normal, Mfx 40% (1 yr); MACI 16% normal/near normal, Mfx 8% (preop.)
ACI vs. OATS							
Dozin ⁴⁰ , 2005	Random permuted block lists	No	Lysholm 1 yr	−0.66 (0.36)	−1.34	0.06	32% (14 of 44) clinically “cured” after AKS debridement; thus, no ACI, OATS. Lysholm complete recovery: 88% OATS, 68% ACI
Horas ⁴² , 2003	Alternating consecutive selection	No	Lysholm 1 yr	−1.01 (0.34)‡	−1.65	−0.34	Lysholm: ACI 25, OATS 28 (preop.); ACI 67, OATS 73 (2 yr) Tegner: ACI 1.6, OATS 1.6 (preop.); ACI 5.1, OATS 5.2 (2 yr)
			Lysholm 2 yr	−0.36 (0.32)	−0.97	0.28	

*ACI = autologous chondrocyte implantation; OATS = osteochondral autograft transfer; Mfx = microfracture; ICRS = International Cartilage Repair Society; IVRS = integrated voice response system; KOOS = Knee Injury and Osteoarthritis Outcome Score; QoL = quality of life; IKDC = International Knee Documentation Committee; RTS = return to sports; CCI = characterized chondrocyte implantation; SF-36 = Short Form-36; AKS = arthroscopic knee surgery. †Effect size is significantly higher than 0 and provides evidence in favor of ACI. ‡Effect size is significantly lower than 0 and indicates evidence against ACI or a different generation of ACI.

TABLE E-7 Study Outcomes Analysis: Intergenerational Comparative ACI Studies (Four Studies)*

	Randomization Method	Independent Clinical Examiner	Outcome Measures	Effect Size (Standard Error)	95% Confidence Interval (Lower)	95% Confidence Interval (Upper)	Summaries
Zeifang ¹⁸ , 2010	Computerized randomization	Yes	IKDC 1 yr (primary)	-0.18 (0.44)	-1.03	0.68	IKDC: MACI 51, PACI 52 (preop.); MACI 72, PACI 77 (1 yr); MACI 70, PACI 77 (2 yr)
			IKDC 2 yr	-0.25 (0.44)	-1.10	0.62	Lysholm: MACI 71, PACI 61 (preop.); MACI 76, PACI 86 (1 yr); MACI 73, PACI 84 (2 yr)
			Lysholm 1 yr	-0.96 (0.46) [†]	-1.82	-0.02	Tegner: MACI 4.1, PACI 3.7 (preop.); MACI 4.2, PACI 4.6 (1 yr)
			Tegner 1 yr	-0.35 (0.44)	-1.20	0.53	
Ferruzzi ⁴¹ , 2008	Not randomized	No	IKDC (objective) 1 yr	0.58 (0.21) [‡]	0.17	0.98	IKDC (subjective): AKS 46, Open 50 (preop.); AKS 88, Open 85 (5 yr)
			IKDC (objective) 5 yr	0.17 (0.20)	-0.23	0.56	IKDC (objective): normal/nearly normal AKS 0%, Open 0% (preop.); normal/nearly normal AKS 100%, Open 90% (5 yr). Open results slower than AKS (AKS more rapid, stabilized at 18 mo)
Gooding ⁴³ , 2006	Sealed envelopes	Yes	Modified Cincinnati 2 yr	0.22 (0.24)	-0.69	0.26	Modified Cincinnati: PACI 62, CACI 67 (preop.); PACI 45, CACI 45 (2 yr)
			ICRS AKS 1 yr	-0.02 (0.26)	-0.53	0.49	Similar macroscopic and histologic examination at 1 yr, 2 yr
			ICRS AKS 2 yr	0.77 (0.46)	-0.17	1.65	36% PACI needed AKS (hypertrophy) vs. 0% CACI at one year
Bartlett ³⁹ , 2005	Sealed envelopes	No	Modified Cincinnati 1 yr	-0.21 (0.21)	-0.62	0.20	Modified Cincinnati: CACI 59, MACI 64 (1 yr); CACI 41, MACI 45 (preop.)
			ICRS AKS 1 yr	0.19 (0.31)	-0.43	0.80	Significantly better modified Cincinnati score: symptomatic <12 mo, <35 yr old

*ACI = autologous chondrocyte implantation; IKDC = International Knee Documentation Committee; MACI = matrix-induced autologous chondrocyte implantation; PACI = periosteal autologous chondrocyte implantation; AKS = arthroscopic knee surgery; ICRS = International Cartilage Repair Society; CACI = Type I/III collagen-membrane autologous chondrocyte implantation. [†]Effect size is significantly lower than 0 and indicates evidence against autologous chondrocyte implantation or a different generation of

autologous chondrocyte implantation. ‡Effect size is significantly higher than 0 and provides evidence in favor of autologous chondrocyte implantation.

TABLE E-8 Study Biases*

Bias (No. of Studies)	Studies
Selection	
Prior surgical interventions (12)	All studies but Dozin ⁴⁰
Inadequate or no randomization (4)	Kon ⁸ , Ferruzzi ⁴¹ , Basad ⁴⁴ , Horas ⁴²
Unequal number subjects in each surgical group	All studies
Performance	
Concurrent procedures (5)	Kon ⁸ , Saris ⁵ , Saris ³⁸ , Zeifang ¹⁸ , Basad ¹⁷
Unknown natural history of chondral defects	All studies
No control group	All studies
Dissimilar, nonstandardized ACL, OATS, MST techniques between studies	All studies
Dissimilar cell therapy manufacturers and cell manipulation techniques	All studies
Transfer	
Attritional bias (1)	Dozin ⁴⁰
Detection	
No use of independent examiners (9)	Saris ⁵ , Kon ⁸ , Ferruzzi ⁴¹ , Knutsen ⁷ , Dozin ⁴⁰ , Bartlett ³⁹ , Basad ⁴⁴ , Basad ¹⁷ , Horas ⁴²
No use of validated outcomes measures (KOOS, IKDC) (6)	Knutsen ⁷ , Knutsen ³⁷ , Gooding ⁴³ , Bartlett ³⁹ , Horas ⁴² , Basad ¹⁷
Lack of long-term follow-up (13)	All studies
Heterogeneous clinical outcome measures	All studies
Heterogeneous outcomes assessment (clinical, arthroscopic, magnetic resonance imaging)	All studies

*ACI = autologous chondrocyte implantation, OATS = osteochondral autograft transfer, MST = marrow-stimulation technique, KOOS = Knee Injury and Osteoarthritis Outcome Score, IKDC = International Knee Documentation Committee.