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James H. Lubowitz, David Appleby, Joseph M. Centeno, Shane K. Woolf and John B. Reid, III

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The Relationship Between the Outcome of Studies of Autologous Chondrocyte Implantation and the Presence of Commercial Funding

James H. Lubowitz,*† MD, David Appleby,‡ MPH, Joseph M. Centeno,† MD, Shane K. Woolf,† MD, and John B. Reid III,† MD
From the †Taos Orthopaedic Institute Research Foundation, Taos, New Mexico, and ‡Smith & Nephew, Andover Massachusetts

Background: Autologous chondrocyte implantation (ACI) is an expensive treatment option for focal cartilage defects, and commercial funding of research is associated with a study reaching a positive conclusion. The purpose of this analysis is to compare outcomes (and levels of evidence) between published ACI outcome studies that were commercially funded and studies that were not commercially funded.

Hypothesis: Commercially funded ACI literature could be commercially biased.

Study Design: Comparative meta-analysis.

Methods: MEDLINE was searched for human, knee, ACI, nonmembrane, English language, and clinical outcome studies. Studies were evaluated with regard to funding status (commercially funded or not commercially funded), outcomes, and levels of evidence. Outcomes and levels of evidence were evaluated and compared for commercially funded studies versus those that were not commercially funded.

Results: Twenty-three studies were included; 16 (70%) were commercially funded. Pooled clinical outcome measures data were not significantly different (Lysholm, Modified Cincinnati, patient-reported Cincinnati, Tegner, pain Visual Analog Scale) when comparing commercially funded studies with those that were not commercially funded. However, distribution of levels of evidence was significantly lower ($P = .045$) for commercially funded studies.

Conclusion: Reassuringly, commercial funding of ACI studies did not result in a difference in published clinical outcomes versus those that were not commercially funded. However, the lower levels of evidence of commercially funded studies suggests that commercially funded ACI studies may be of less value to surgeons desiring to practice evidence-based medicine, and, in the future, commercial entities funding medical research could selectively fund studies of the highest levels of evidence.

Keywords: autologous chondrocyte implantation; autologous chondrocyte transplantation; meta-analysis; bias; funding; commercial.

Treatment of focal articular cartilage defects remains a complex problem for orthopaedic surgeons and their patients. These lesions have a low capacity for healing and may progress to osteoarthritis over time.[17] Pain relief is the primary indication for surgical treatment of these lesions; a secondary aim is retarding articular cartilage degeneration. Treatment options for patients with focal cartilage defects include microfracture, osteochondral autograft (or allograft) transplantation, and autologous chondrocyte implantation (ACI). Autologous chondrocyte implantation involves autologous chondrocyte biopsy, subsequent chondrocyte culturing with expansion of the number of cells, and, ultimately, chondrocyte reimplantation into a focal cartilage defect.[6]

Since its inception more than 16 years ago, ACI has gained increasing acceptance as a treatment option for symptomatic, full-thickness focal cartilage defects.[5,6,24] Although ACI is reported to be an expensive therapy,[9]

*Address correspondence to James H. Lubowitz, MD, Taos Orthopaedic Institute, 1219-A Gusdorf Rd, Taos, NM 87571 (e-mail: jlubowitz@kitcarson.net).

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Level I evidence indicates that ACI outcomes may be no better than outcomes of the least invasive, least costly, cartilage restoration procedure, microfracture.[19] With this in mind, and in the context of recent suggestion in the medical and orthopaedic literature of an association between commercial funding and a study arriving at a positive conclusion,[20,21] we hypothesize that ACI published outcome literature may be commercially biased.

Meta-analysis is a study design that allows us to test this hypothesis. Meta-analytic techniques allow quantitative statistical pooling of results from different studies. Thus meta-analysis allows determination of efficacy of ACI in commercially funded studies and studies that were not commercially funded, respectively. Then, a comparison of the results of published ACI outcome studies that were commercially funded with studies that were not commercially funded is possible.

The purpose of this investigation is to compare outcomes (and as a secondary measure, levels of evidence) between published ACI outcome studies that were commercially funded and published outcome studies that were not commercially funded. As above, we hypothesize that commercially funded studies will report better outcomes.

MATERIALS AND METHODS

In December 2005, medical literature relevant to ACI was identified by searching the National Library of Medicine's MEDLINE and preMEDLINE database (PubMed/MEDLINE) using the search terms *chondrocytes*, *transplantation*, *implantation*, and *autologous* as specified in Figure 1. Excluded were nonhuman studies, non-English-language studies, studies related to joints other than the knee joint, cadaveric studies, biomechanical studies, membrane-ACI studies, letters, expert opinion publications, case reports, studies with nonclinical outcomes, and reviews of prior published data. In studies where we could determine that a single cohort of patients was reported in more than 1 publication, only the most recent publication was included.

Studies that disclosed commercial funding (defined as any disclosure of any author financial relationship to a commercial entity related to the topic of the study) were classified as commercially funded. Studies disclosing government grants or grants supported by an academic institution were considered as not commercially funded. Studies that did not disclose commercial funding or specifically reported no commercial funding were initially considered not commercially funded. However, with regard to studies initially considered as not commercially funded (index unfunded), if any of the index unfunded study authors were also authors of other published studies that did disclose commercial funding, then such index unfunded studies were reclassified as commercially funded.

All authors of our article individually reviewed each included study and documented commercial funding status, level of evidence, and reported clinical outcomes. Reported clinical outcomes were analyzed for outcome measures that were reported in multiple studies (so as to allow comparison between studies), and outcome measures that were reported in multiple studies were selected for evaluation. A final review was performed by all authors, and a consensus was reached on all extraction items.

1. chondrocytes/transplantation [mesh]
2. transplantation, autologous [mesh]
3. 1 AND 2
4. autologous [tw] AND chondrocyte [tw]
5. transplantation [tw] OR implantation [tw]
6. 4 AND 5
7. autologous [tw]
8. 1 AND 7
9. 3 OR 6 OR 8
10. limit 9 to human
11. limit 10 to English [1a]

Figure 1. PubMed/MEDLINE search strategy: the terms *chondrocytes*, *transplantation*, *implantation*, and *autologous* were searched as enumerated.

Because our investigation includes evaluation of the potential for commercial bias in the orthopaedic literature, it is relevant to disclose that more than 1 of the authors of our article has received something of financial value from more than 1 commercial entity that supports surgical techniques that may be deemed commercially competitive with ACI (ie, microfracture, osteochondral autograft or allograft transplantation, joint replacement arthroplasty); none of the authors have received something of financial value from a commercial entity that supports ACI. In addition, it is relevant to note that none of the authors of our article are involved, nor have been involved, in legal or other conflicts related to any of these techniques or related to any commercial entity related to the topic of our investigation.

Statistical Methods

For each outcome measure selected for evaluation, mean improvement in outcome and an associated 95% confidence interval were calculated for each study that reported the measure. In addition, for each outcome measure, an overall mean and associated confidence interval was calculated for commercially funded studies and separately for studies that were not commercially funded. A random effects model, as described by Sutton et al,[35] was used to estimate the overall mean for each outcome measure.

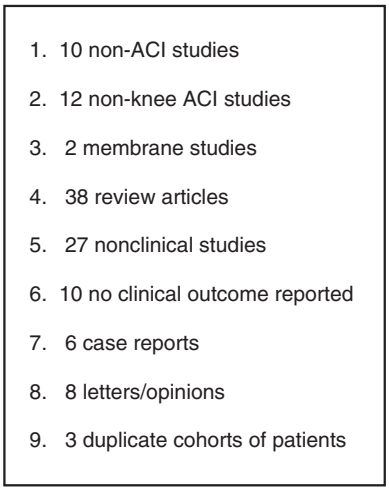

Figure 2. Of 139 published articles identified in the literature search, 116 were excluded. Reasons for exclusion are quantified as enumerated.

When using a random effects model, the overall mean is weighted by the inverse of the sum of the between-study and within-study variances. A random effects model was selected to account for heterogeneity in the design or patient selection among included studies.

With regard to level of evidence, a χ^2 analysis using the Fisher exact test was performed to determine if there was a difference in the distribution of levels of evidence for commercially funded studies as compared with studies that were not commercially funded.

RESULTS

A total of 139 published articles were identified in the literature search. After application of the inclusion criteria, a total of 23 publications* were included. Reasons for published article exclusion are summarized in Figure 2.

Sixteen (70%) of the included studies were categorized as commercially funded, and 7 (30%) of the published ACI studies were categorized as not commercially funded.

Clinical outcome measures reported in multiple studies (allowing comparison between studies) were Lysholm score (reported in 5 funded studies and 4 unfunded studies), Modified Cincinnati score (reported in 2 funded studies and 1 unfunded study), patient-reported Cincinnati score (reported in 11 funded studies and 1 unfunded study), Tegner score (reported in 6 funded studies and 3 unfunded studies), and pain visual analog score (VAS) (reported in 2 funded studies and 3 unfunded studies). Table 1 lists the

*References 1, 3, 4, 6, 7, 10, 11, 14-16, 19, 23-27, 29-31, 33, 36, 37, 39.

TABLE 1
Summary of Included Studies[a]

Author(s) (Year)	Commercial Funding	Level of Evidence	Number of Subjects	Outcomes
Bartlett et al[1] (2005)	Yes	II	44	Visual analog pain score
Bentley et al[3] (2003)	Yes	I	58	Good/excellent outcome
Brittberg et al[6] (1994)	Yes	IV	23	Good/excellent outcome
Browne et al[7] (2005)	Yes	IV	87	Patient Cincinnati score, improvement
Henderson et al[15] (2003)	Yes	IV	57	Improvement
Henderson et al[14] (2005)	Yes	IV	54	IKDC classification
Lindahl et al[23] (2001)	Yes	IV	57	Good/Excellent Outcome
Micheli et al[24] (2001)	Yes	IV	50	Modified Cincinatti score, patient Cincinatti score, improvement
Minas and Bryant[25] (2003)	Yes	IV	169	Patient Cincinnati score
Minas and Bryant[26] (2005)	Yes	IV	45	Good/excellent outcome
Mithofer et al[27] (2005)	Yes	IV	20	Lysholm score, Tegner score, good/excellent outcome
Peterson et al[31] (2000)	Yes	IV	101	Lysholm score, improvement
Peterson et al[29] (2002)	Yes	IV	61	Patient Cincinnati score, Tegner score, good/excellent outcome
Peterson et al[30] (2003)	Yes	IV	58	Patient Cincinnati score, Lysholm score, Tegner score, visual analog pain score, good/excellent outcome
Vasara et al[36] (2005)	Yes	IV	32	Good/excellent outcome
Yates[39] (2003)	Yes	IV	10	Modified Cincinatti score, patient Cincinatti score, good/excellent outcome
Briggs et al[4] (2003)	No	IV	14	Lysholm score, Tegner score, visual analog pain score, improvement
Dozin et al[10] (2005)	No	I	22	Success/failure
Erggelet et al[11] (2000)	No	IV	24	Modified Cincinatti score, patient Cincinatti score, improvement
Horas et al[16] (2003)	No	II	30	Lysholm score, Tegner score, improvement
Knutson et al[19] (2004)	No	I	40	Lysholm score,visual analog pain score
Robinson et al[33] (2000)	No	IV	8	Visual analog pain score
Visna et al[37] (2004)	No	I	25	Lysholm score, Tegner score

[a]IKDC, International Knee Documentation Committee.

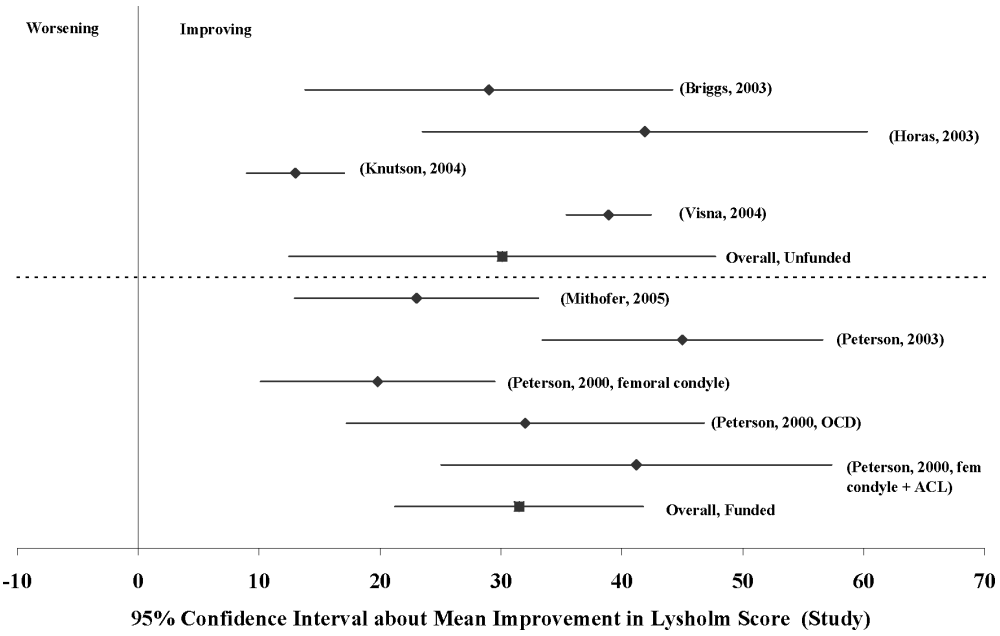

Figure 3. Mean Lysholm score and 95% confidence intervals by study (bibliographical reference in parentheses) and overall. (Studies that were not commercially funded and Overall, Unfunded appear above the dotted horizontal line; commercially funded studies and Overall, Funded appear below the dotted horizontal line.) OCD, osteochondritis dissecans.

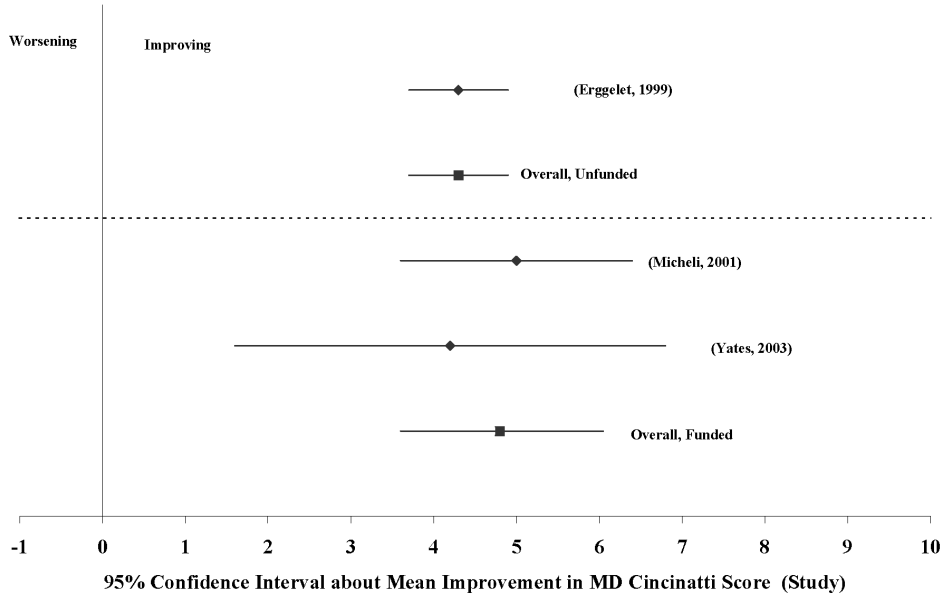

Figure 4. Mean Modified Cincinnati score and 95% confidence intervals by study (bibliographical reference in parentheses) and overall. (Studies that were not commercially funded and Overall, Unfunded appear above the dotted horizontal line; commercially funded studies and Overall, Funded appear below the dotted horizontal line.) MD, Modified.

included studies, commercial funding status, levels of evidence, and reported clinical outcome measures allowing study comparison.

The pooled clinical outcome measure data were not significantly different (overlapping 95% confidence intervals) when comparing the commercially funded studies and the studies that were not commercially funded. The overall improvement in Lysholm score in the commercially funded studies was 31.5 compared with 30.1 in the studies that were not commercially funded (Figure 3). The overall improvement in Modified Cincinnati score in the commercially funded studies was 4.8 compared with 4.3 in the study that was not commercially funded (Figure 4). The overall improvement in patient-reported Cincinnati score in the

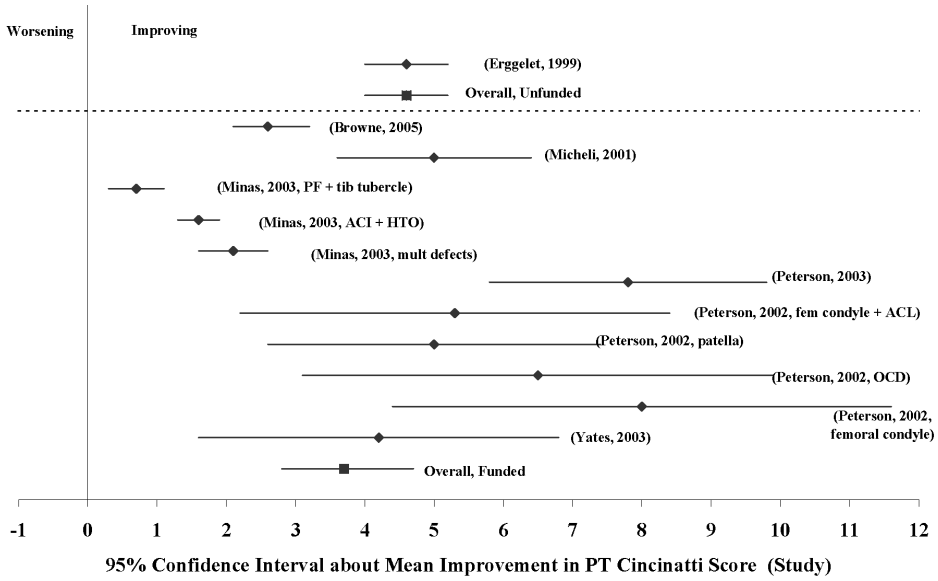

Figure 5. Mean patient-reported Cincinnati score and 95% confidence intervals by study (bibliographical reference in parentheses) and overall. (Studies that were not commercially funded and Overall, Unfunded appear above the dotted horizontal line; commercially funded studies and Overall, Funded appear below the dotted horizontal line.) PT, patient; PF, patellofemoral; ACI, autologous chondrocyte implantation; HTO, high tibial osteotomy; ACL, anterior cruciate ligament; OCD, osteochondritis dissecans.

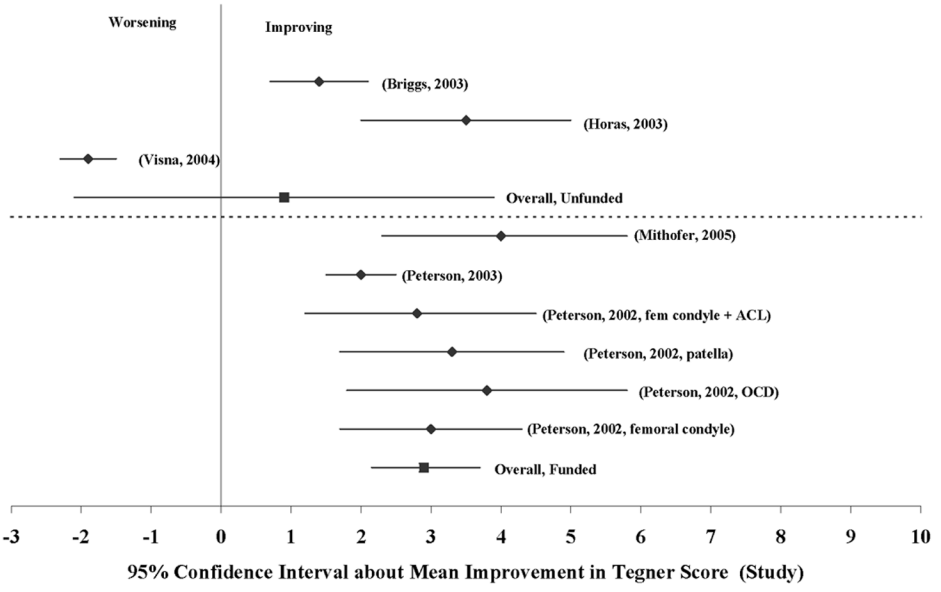

Figure 6. Mean Tegner score and 95% confidence intervals by study (bibliographical reference in parentheses) and overall. (Studies that were not commercially funded and Overall, Unfunded appear above the dotted horizontal line; commercially funded studies and Overall, Funded appear below the dotted horizontal line.) ACL, anterior cruciate ligament; OCD, osteochondritis dissecans.

commercially funded studies was 3.7 compared with 4.6 in the study that was not commercially funded (Figure 5). The overall improvement in Tegner score in the commercially funded studies was 2.9 compared with 0.9 in the studies that were not commercially funded (Figure 6). The overall improvement in pain VAS in the commercially funded studies was 3.2 compared with 3.7 in those that were not commercially funded (Figure 7).

With regard to level of evidence, 88% (14 of 16) of the commercially funded studies were Level IV evidence (case series), while only 6% (1 of 16) were Level I evidence and 6% (1 of 16) were Level II evidence. In comparison, 43% (3 of 7) of the studies that were not commercially funded were Level I evidence (randomized controlled trials), and 14% (1 of 7) were Level II evidence (prospective comparative study); 43% (3 of 7) of studies that were not commercially funded

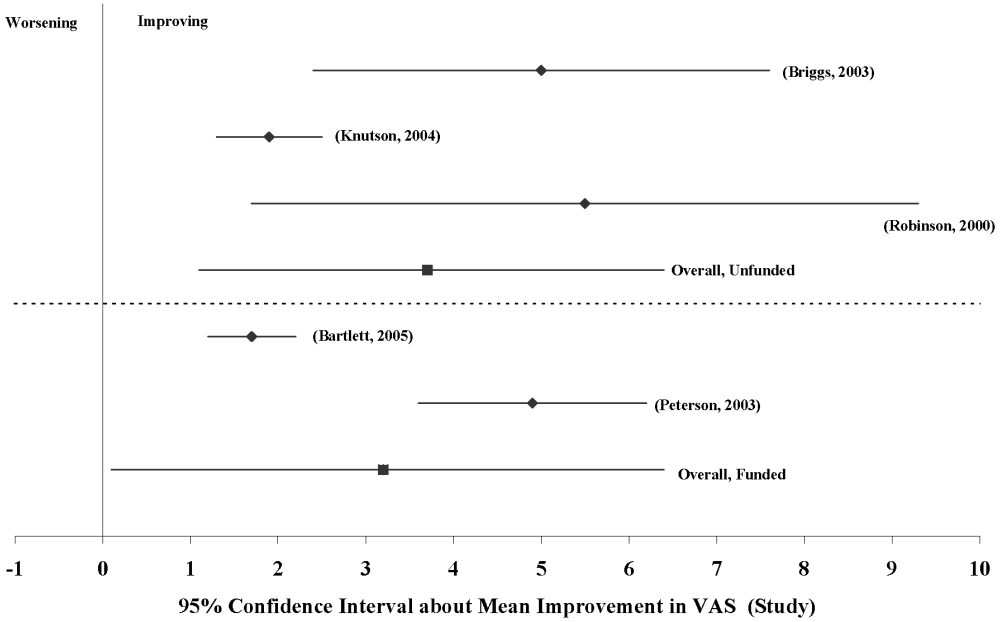

Figure 7. Mean pain VAS and 95% confidence intervals by study (bibliographical reference in parentheses) and overall. (Studies that were not commercially funded and Overall, Unfunded appear above the dotted horizontal line; commercially funded studies and Overall, Funded appear below the dotted horizontal line.) VAS, Visual Analog Scale.

TABLE 2
Levels of Evidence by Commercial Funding Status

	Commercial Funding	
Level of Evidence	Yes	No
I	3 (43%)	1 (6%)
II	1 (14%)	1 (6%)
III	0	0
IV	3 (43%)	14 (88%)

were Level IV evidence. In summary, the distribution of levels of evidence revealed lower levels of evidence (P = .045) for commercially funded studies as compared with studies that were not commercially funded (Table 2).

DISCUSSION

Our results demonstrate that a difference in published clinical outcomes comparing commercially funded ACI studies and those that were not commercially funded was not observed. This finding may differ from other published literature evaluating the effect of commercial funding on study outcomes.

Both the expense of research and limited funding sources have forced an increased reliance on commercial support for medical research, introducing the potential for bias.[20] Commercial research grants are often accompanied by contracts that include restrictive covenants, permitting the corporate sponsor to prevent publication of negative results.[32] The association between funding source and study outcome has been researched by various medical specialties.[2,8,12,13,22,28,32,38] Only recently has the orthopaedic literature evaluated this subject. In 2003, Leopold et al[21] reviewed articles published in 3 orthopaedic journals (*The Journal of Bone and Joint Surgery–American,* the *Journal of Arthroplasty,* and *The American Journal of Sports Medicine*) in 1999 and 2000. Those authors found that commercial funding was associated with positive study outcome but clarified that this did not imply the presence of a corrupting or causative influence. Leopold et al called for additional research to determine whether such nonscientific factors actually affect study outcome. In 2005, Shah et al[34] reviewed articles published in *Spine* from 2002 to July 2003. Those authors also found that commercial funding was associated with positive study outcome, and they hypothesized potential explanations of bias in study design, bias in experimental technique, bias in result interpretation, or publication bias. Our results differ from the findings of both Leopold et al and Shah et al. Although we are unable to explain the reason for this difference, we do believe our results to be reassuring with regard to commercial funding of ACI investigation.

With regard to levels of evidence, commercially funded studies demonstrated significantly lower levels of evidence. In the opinion of the authors, commercial entities funding medical research could, in the future, selectively aspire to fund studies of the highest levels of evidence. Prospective comparative studies (level II evidence) or randomized controlled trials (level I evidence) could be recommended. This is consistent with other publications that

implore cartilage investigators to perform randomized controlled trials.[18]

Our study has limitations. Heterogeneity of the included studies presents a challenge regarding comparison or synthesis of published results. Published studies differ from each other with regard to surgeons, resulting in performance bias. Published studies differ both with regard to location of chondral injury within the knee joint and with regard to the demographics of the study cohort. These factors may result in selection bias as different patients or different cohorts may have different prognoses. Published studies differ with regard to outcome measures (reporting bias). We have attempted to minimize the effects of study heterogeneity through the use of a random effects statistical model. Nevertheless, differences among groups compared still exist. This is consistent with a previous report that criticized both methodology and quality of published cartilage repair studies.[18]

An additional limitation is that non-English-language articles were excluded from this investigation. It is possible that the inclusion of non-English-language articles would change our results. Our other study exclusion criteria may also represent limitations. Similarly, we searched only a single database limited to published articles. It is possible that other search criteria would change our results.

Our method for reclassifying index unfunded studies may be controversial. However, these methods were selected because we believe it could be possible that authors who even once received commercial funding for an ACI study could be commercially biased. An additional limitation is that some authors of studies classified as not commercially funded may actually have commercial relationships that were not disclosed. Also, we acknowledge above that some of the authors of this study have commercial relationships; our methods are designed to minimize commercial or other bias on the part of the investigators.

Another limitation resulting from reporting bias (heterogeneity of outcome measures) among the included studies was small sample sizes for any 1 specific clinical outcome measure. Uniformity of outcome measures used in studies of ACI would allow for larger numbers of studies to pool for a particular outcome measure, leading to better estimates of effect size. This lack of uniformity has been noted previously.[18] Similarly, the small number of ACI studies that were not commercially funded results in relatively wide confidence intervals. A greater number of studies included in the analysis would provide narrower confidence intervals, with a more precise estimate of effect size.

In conclusion, our hypothesis was not supported. Rather, a difference in published clinical outcomes comparing commercially funded ACI studies and ACI studies that were not commercially funded was not observed. In addition, our results demonstrate that the levels of evidence of commercially funded ACI studies are lower than the levels of evidence of ACI studies that were not commercially funded. This finding suggests that commercially funded ACI studies may be of less value to surgeons desiring to practice evidence-based medicine, and future commercially funded studies should incorporate higher levels of evidence in their design.

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