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# A Randomized Multicenter Trial Comparing Autologous Chondrocyte Implantation with Microfracture

## Long-Term Follow-up at 14 to 15 Years

Gunnar Knutsen, MD, PhD; Jon Olav Drogset, MD, PhD; Lars Engebretsen, MD, PhD; Torbjørn Grøntvedt, MD, PhD; Tom C. Ludvigsen, MD; Sverre Løken, MD, PhD; Eirik Solheim, MD, PhD; Torbjørn Strand, MD; Oddmund Johansen, MD, PhD

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# ICRS Commentary on the Study by Knutsen et al.*

**Tom Minas, Orthopedic Surgeon Brigham and Women's Hospital, Boston, USA; International Cartilage Repair Society, 2nd Vice President**

*Additional signatories to this eLetter are Leela Biant, MD; Mats Brittberg, MD, PhD; Brian Cole, MD; Christoph Erggelet, MD; Jack Farr, MD; Alberto Gobbi, MD; Andreas H. Gomoll, MD; Elizaveta Kon, MD; Christian Lattermann, MD; Henning Madry, MD; Norimasa Nakamura, MD; Stefan Nehrer, MD; Lars Peterson, MD, PhD; Daniel Saris, MD; and Kenneth Zaslav, MD.

We reviewed the Knutsen et al. article with great interest. In addition, the excellent commentary by Dr. Freddie Fu and Dr. Ashish Soni (1) touches on many valid points related to the comparison of autologous chondrocyte implantation (ACI) versus microfracture. Of particular importance is the correction that the cartilage biopsy for cell culture is performed arthroscopically and not by mini-arthrotomy as they describe in their commentary.

Knutsen et al. are to be commended for performing a randomized clinical trial (RCT) for evaluation of two different surgical techniques for cartilage repair. However, we have several concerns. Most significantly, the authors state in this paper that “No long-term results exist. So far, that study [Vanlauwe et al.; see reference 11 below] does not prove that the cell cultivation performed in vitro improves the outcome.”

Given the abundance of existing literature sighting excellent outcomes following ACI, we remain concerned that some of this article’s language may lead to unintended consequences for regulatory bodies and payers and potentially limit the availability of what has largely been proven to be an excellent treatment option for our patients. For this reason, members of the International Cartilage Repair Society (ICRS), who perform cartilage repair and utilize cell cultivation for treatment of large articular injuries, wish to comment on this article.

Most cartilage repair surgeons, as well as peer-reviewed clinical outcomes, support the use of cultured articular chondrocytes for large articular lesions greater than 4 $cm^2$ (2,3,4,5,6). When measuring articular cartilage injuries arthroscopically, it has been shown that inexperienced surgeons oversize the lesions relative to when direct measurements are obtained at the time of an open arthrotomy (7). Hence, an arthroscopic-only procedure such as microfracture is likely to be treating lesions of smaller size compared to ACI, potentially skewing the results in favor of a population of patients known to respond favorably to marrow stimulation.

In addition, the "learning curve" to perform ACI versus microfracture is quite different. Harvesting periosteum from the proximal tibia is tedious and requires meticulous technique. The harvested tissue is prone to tearing when it is microsutured to the articular cartilage. Obtaining a watertight defect and seal is an additional challenge related to this procedure. (Contemporary ACI does not use periosteum and results are likely better with a TypeI/III collagen membrane.) Microfracture is an established arthroscopic technique that surgeons find straightforward, simple, and efficient to perform. The technical challenge of ACI may negatively affect the outcome of ACI and may be a reason for worse failure rates noted in the Knutsen study. The 60% ACI failure rate at one of the four centers is worrisome and could be associated with the performance of ACI by less experienced surgeons still learning the technique. Notably, the experience of Minas et al. was that the failure rate of ACI performed in knees that had not undergone prior microfracture was only 8% (8).

Knutsen's 15-year cohort demonstrated that osteoarthritis identified at follow-up could not be avoided by cartilage repair, whether by ACI or microfracture; 57% (ACI) versus 48% (microfracture) had Kellgren and Lawrence grade of >=2. This is an alarming rate of OA; after 5 years in Knutsen's cohort there was only a 25% incidence of OA. This emphasizes the need for and the lack of a non-operative treatment arm in the study (9). Also, other factors for OA were not captured such as BMI and long leg alignment. The authors cannot exclude that natural degeneration explains part of the findings. This point has been emphasized by Koster et al. (10) in following patients with traumatic knee injuries.

This study questioned whether cell cultivation was worthwhile as the clinical outcomes comparing ACI to microfracture were not different. Contrary to the findings in the Knutsen study, there have been two European, multicenter RCTs that had larger patient numbers and more complete follow-up. These results favored ACI over microfracture. One study used first-generation ACI with pre-selected chondrocytes (11). In the second trial, a third-generation matrix-based ACI showed clear benefit over microfracture in defects larger than 3 $cm^2$ (12).

We believe that the study by Knutsen et al. does not represent a real-world scenario of the universe of patients who can benefit from ACI. Supporting this contention is the corresponding author's 20-year database at the Brigham and Women's Hospital's Cartilage Repair Center Registry in Boston, which contains more than 800 patients treated with ACI. Only 37 patients in the registry had a neutrally aligned, stable knee, with intact meniscus and a single defect average size of 4.5 $cm^2$. Six of these patients with defects <4.5$cm^2$ have greater than 20 year follow up, and none have failed to date. These are the same patients who meet the inclusion criteria in current multicenter RCTs, yet they only represent a fraction of the patients that can benefit from cell culturing. The vast majority of patients have more than one defect, comorbidities, and lesions on all surfaces of the knee that respond well to ACI. In addition, there are few treatments that effectively and predictably treat the patellofemoral joint other than ACI (13,14,15) with greater than 80% patient satisfaction and good to excellent results where microfracture otherwise fares poorly (16).

In Knutsen's study, the defect sizes averaged 4.5 cm (range 1.44–11.25 $cm^2$), but it is not known among which group the outliers were. Long alignment films were not done at baseline, and there were 8 failures, 4 in each group, salvaged by osteotomy. This leads us to question the definition of failure as poor clinical response or repair-site delamination, breakdown, or other mechanism not defined in the article. Notably, some of the best long-term outcomes are when ACI is combined with a re-alignment procedure, with 90% survivorship at 15 years (5).

The concept that microfracture doesn't "burn bridges" and is a straightforward procedure with benign consequences has proven to be untrue. Microfracture (MFX) does burn bridges when it comes to the treatment of failed MFX treatments with ACI, because the failure rate is 3 to 6 times worse than a primary ACI without prior violation of the subchondral bone (8,17,18). Arthroscopic chondroplasty versus microfracture would be a worthwhile randomized controlled trial design, as these are the usual treatments that are performed by cartilage repair surgeons for small lesions. In fact, return to play after microfracture in NFL football players (19) was 4.4 times less likely than if treated by simple chondroplasty, regardless of lesion size or location. There is ample evidence that synovial stem cells (20,21) may also be involved in the repair response and may migrate to the site of injury for the repair of small articular injuries where violation of the subchondral bone may not be necessary.

We agree with much of Drs. Fu and Soni's closing statements: "As the evidence stands currently, microfracture has favorable results for small (<=4 $cm^2$), contained chondral defects. ACI has more favorable outcomes than microfracture for larger, contained defects. Management of these defects should be individualized…" However "small" lesions should be clarified. Prior published algorithms (22,23) have emphasized defects 2 $cm^2$ or less for microfracture and other studies (12,16) less than 3 $cm^2$. Finally, we should add that the relative size of the defect is

important as 4 cm² in the smaller knee may represent almost the entire weight bearing surface, compared to the same defect in a larger individual. This emphasizes the importance of individualized assessment and treatment.

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