

# Editorial Commentary: Bone Marrow Aspirate Concentrate May Accelerate Anterior Cruciate Ligament Allograft Using Bone Patellar Tendon Bone Maturation on Magnetic Resonance Imaging, but Clinical Differences Have Not Been Demonstrated



Andrew J. Sheean, M.D., Associate Editor

**Abstract:** Accelerating graft healing in anterior cruciate ligament reconstruction (ACLR) continues to be an elusive proposition. In vivo assessments of graft histology are challenging to perform, especially in human subjects. Multiple authors have reported on the utility of magnetic resonance imaging as a noninvasive modality in characterizing post-operative changes, suggestive of graft maturation. However, previous literature, by and large, has been limited by heterogenous scanning protocols and underpowered comparisons of dissimilar treatment techniques, and these issues complicate efforts to assess the benefits (if any) of adjuncts focused on improving graft healing after ACLR. Particularly in cases of allograft ACLR, where concerns persist regarding the pace and quality of tissue healing and graft integration, the use of orthobiologic adjuncts represents a promising area for ongoing investigation. Although there has been great enthusiasm for the use of bone marrow aspirate concentrate as an adjunct in a variety of applications, high level evidence substantiating its use in ACLR is lacking. Even when significant differences between groups treated with and without such adjuncts may be apparent radiographically, demonstrating a concrete, clinical benefit will continue to be a difficult proposition.

See related article on page 2255

Most of us are inclined to swing for the fences, and undertaking randomized controlled trials presents the allure of answering clinical questions decisively. However, these studies are hard to execute. Their design requires focused attention to a number of considerations: Who should be included (and excluded)? What kinds of treatments should be compared? Which outcomes should be measured, and how should those assessments be performed? Given the typical scope of such efforts and the exposure of

patients to different treatment interventions, the knowledge gap that the proposed research seeks to address should be substantial, and the immediate impact of the study's principal findings should be robust. Or should it? Must all innovation occur through the release of disruptive, "game-changing" findings? I'm sure you can tell by the way I'm framing these questions that I think the answer is "no", and as much as those of us who are involved in clinical research would like to be involved in something that definitively answers a particular question, we should not discount the value of research that meaningfully contributes to the growth of knowledge in a more incremental way. Stated differently and not done so in a way to suggest that knowledge gained incrementally is the byproduct of less ambitious effort, can't we still get excited about data and conclusions that are likened to singles rather than home runs? The current study, entitled "Bone Marrow Aspirate Concentrate Augmentation May Accelerate Allograft Ligamentization in Anterior Cruciate Ligament Reconstruction: A Double-Blinded,

*The author reports the following potential conflicts of interest or sources of funding: A.J.S. has received grants from Embody, AOSSM, and CDMRP. A.J.S. is a committee or board member of the Society of Military Orthopaedic Surgeons, Arthroscopy Association of North America, and American Orthopaedic Society for Sports Medicine and has received personal fees from Arthroscopy. Full ICMJE author disclosure forms are available for this article online, as supplementary material.*

*Published by Elsevier on behalf of the Arthroscopy Association of North America*

0749-8063/22276/\$36.00

<https://doi.org/10.1016/j.arthro.2022.03.016>

Randomized Controlled Trial” by Forsythe, Chahla, Korrapati, Lavoie-Gagne, Forlenza, Diaz, Chung, Bae, Bach, Cole, Yanke, and Verma, provides us with important information relevant to the orthobiologics space and reminds us that the pursuit of knowledge is, generally speaking, iterative and incremental.<sup>1</sup>

This study sought to determine whether the addition of bone marrow aspirate concentrate (BMAC) to allograft bone patellar tendon bone (BTB) anterior cruciate ligament (ACL) reconstruction (ACLR) improves graft maturation at 3 and 9 months postoperatively. The authors powered the study to detect a meaningful difference in the signal intensity ratios (SIRs) of grafts on magnetic resonance imaging (MRI), and, in fact, significantly increased SIRs were observed in the BMAC group at 3 months postoperatively. However, these differences were not sustained when MRI was repeated at 9 months postoperation. The authors further observed significantly higher International Knee Documentation Committee (IKDC) scores among subjects in the BMAC group between groups at 9 months postoperation, but the authors also acknowledge that the proportion of subjects achieving the minimal clinically important difference for the IKDC was not significantly different between groups.

To their credit, Forsythe et al. successfully executed this randomized, controlled surgical trial, which was also recognized with the Richard O’Connor Research Award at the 2021 combined American Orthopaedic Society for Sports Medicine-Arthroscopy Association of North America Annual Meeting. It is a focused and well-designed study to answer a discrete question. Given the fact that previously published literature suggests that allografts used in ACLR may undergo incomplete and/or delayed vascularization and ligamentization,<sup>2</sup> the addition of an orthobiologic treatment in this setting would appear to be a potentially useful adjunct to accelerate tissue healing.<sup>3</sup> As such, results should pique our attention. Recently, Baird et al. performed a level IV systematic review of the published literature focusing on cellular augmentation of ACLR and identified only 4 articles meeting inclusion criteria. Unsurprisingly, a dearth of positive effects has been observed to substantiate the use of cellular augmentation as an adjunct to ACLR.<sup>4,5</sup> In fact, at the time of its publication, this same systematic review identified only one randomized, controlled surgical trial comparing clinical and MRI-based outcomes of ACLR (BTB autograft) augmented with BMAC. So, it is apparent that this space is relatively unexplored and worthy of ongoing investigation.

In several respects, the current study does not deliver results likely to substantively affect the surgeons’ approach to allograft ACLR. After all, one can’t help but ask, “what are the long-term implications of the observed differences in SIRs between the two treatment

groups at 3 months postoperation?” This unsettled matter is important given that 1) the lack of significantly different SIRs between groups at 9 months postoperation, 2) the statistically significant, but *clinically insignificant*, differences in IKDC scores at 9 months postoperation, 3) the lack of significant differences between groups in all other assessed PRO at all other timepoints, 4) the observed differences in SIRs observed at 3 months postoperation were not maintained when MRIs were repeated 6 months later, and 5) there were no differences in anterior-posterior translation in either group, as assessed by KT-1000 measurement. Of note, the authors do not report on failure/retear rates and, is always the case with clinical trials involving ACLR, outcomes at 2 years and beyond go a long way toward helping us to understand the durability of these interventions’ results. Is it possible that the addition of BMAC to allograft BTB exerts an unrecognized effect on clinical outcomes? On the basis of the work of Forsyth et al., I’d be inclined to say “no”. But I also acknowledge that it is impossible to know this for sure given the short-term, follow-up interval and relatively small numbers of patients in each group, which were undersized to answer this question definitively.

Questions beget more questions, and in the hands of capable researchers, the pursuit of answers can compel a particular flavor of innovation, one that is deliberate and not necessarily punctuated by earth-shattering conclusions. We ought not interpret the findings of one study, particularly one in which the results are mixed, as a justification for abandoning the search for clarity in a particular topic area. Worse yet would be the dismissal of a study’s results as being of minimal clinical utility. The current study showed that *something* is, indeed, going on in the allografts treated with BMAC, but what, exactly? Increased vascularization in isolation? Vascularization associated with accelerated/improved ligamentization? More work needs to be done to evaluate histological changes, which is suggestive of graft maturation as a function of graft vascularity in humans. As van Groningen et al. have shown in a systematic review of 13 published reports relating to the use of postoperative MRI to assess graft appearance, the heterogeneity in MRI scanning protocols has obscured concrete characterizations of graft healing and maturation.<sup>6</sup> Clearly, additional investigation into the utility of MRI for characterizing dynamic changes in ACLR graft biology is warranted.

Ultimately, I assess the importance of Forsythe et al.’s work as an important contribution to an existing body of literature focused on both the optimization of the conditions for ACL graft healing and the surveillance of graft maturation postoperatively. The recognition of BMAC’s effect on graft biology in the early postoperative period represents incremental progress that, in a more general sense, has been characteristic of the

growth of evidence supporting the use of orthobiologic therapies in a variety of clinical scenarios. Yes, home runs bring everyone to their feet, but so too can singles, especially when there are runners in scoring position.

### References

1. Forsythe B, Chahla J, Korrapati A, et al. Bone marrow aspirate concentrate augmentation may accelerate allograft ligamentization in anterior cruciate ligament reconstruction: A double-blinded randomized controlled trial. *Arthroscopy* 2022;38:2255-2264.
2. Panos JA, Webster KE, Hewett TE. Anterior cruciate ligament grafts display differential maturation patterns on magnetic resonance imaging following reconstruction: A systematic review. *Knee Surg Sports Traumatol Arthrosc* 2020;28:2124-2138.
3. Guo R, Gao L, Xu B. Current evidence of adult stem cells to enhance anterior cruciate ligament treatment: A systematic review of animal trials. *Arthroscopy* 2018;34:331-340. e332.
4. Baird JPE, Anz A, Andrews J, et al. Cellular augmentation of anterior cruciate ligament surgery is not currently evidence based: A systematic review of clinical studies. *Arthroscopy*. *Arthroscopy* 2022;38:2047-2061.
5. Hunt TJ. Editorial commentary: Animal trials using stem cells to enhance anterior cruciate ligament treatment are interesting. but, why not more about us humans? *Arthroscopy* 2018;34:343-344.
6. van Groningen B, van der Steen MC, Janssen DM, van Rhijn LW, van der Linden AN, Janssen RPA. Assessment of graft maturity after anterior cruciate ligament reconstruction using autografts: A systematic review of biopsy and magnetic resonance imaging studies. *Arthrosc Sports Med Rehabil* 2020;2:e377-e388.