AAOS
American Academy of Orthopaedic Surgeons

Concentrated Bone Marrow Aspirate for Knee Osteoarthritis Technology Overview

Review Period Report

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Concentrated Bone Marrow Aspirate for Knee Osteoarthritis

Overview of the Review Period

The reviews and comments related to this technology overview are reprinted in this document and posted on the AAOS website. All reviewers are required to disclose their conflict of interests.

Review Process:

AAOS contacted 5 organizations with content expertise to review a draft of the technology overview during the three-week peer review period in July 2021.

Additionally, the draft was also provided to members of the AAOS Board of Directors (BOD), members of the Council on Research and Quality (CORQ), members of the Board of Councilors (BOC), members of the Board of Specialty Societies (BOS) and members of the Committee on Evidence-Based Quality and Value (EBQV) for review and comment.

- Five (5) individuals provided comments via the electronic structured peer review form. No reviewers asked to remain anonymous.
- All five reviews were on behalf of a society and/or committee.
- The work group considered all comments and made some modifications when they were consistent with the evidence.

Reviewer Key

Each reviewer was assigned a number (see below). All responses in this document are listed by the assigned peer reviewer's number.

Table 1. Reviewer Key

Reviewer Number	Name of Reviewer	Society/ Committee Being Represented
1	Seth Sherman	American Orthopaedic Society for Sports Medicine
2	Alberto Gobbi	International Cartilage Regeneration & Joint Preservation Society
3	Matthew Abdel	AAOS Board of Directors
4	Aidin Eslam Pour	American Association of Hip and Knee Surgeons
5	Jorge Chahla	Arthroscopy Association of North America

Reviewer Demographics

Table 2: Reviewer Demographics

Reviewer Number	Name of Reviewer	Primary Specialty	Work Setting
1	Seth Sherman	Sports Medicine	Academic Practice
2	Alberto Gobbi	Sports Medicine	Private Group or Practice
3	Matthew Abdel	Adult Hip	Academic Practice
4	Aidin Eslam Pour	Adult Hip	Academic Practice
5	Jorge Chahla	Sports Medicine	

Reviewers' Disclosure Information

All reviewers are required to disclose any possible conflicts that would bias their review via a series of 10 questions (see Table 3). For any positive responses to the questions (i.e. "Yes"), the reviewer was asked to provide details on their possible conflict.

Table 3. Disclosure Question Key

Disclosure Question	Disclosure Question Details
A	A) Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device?
B	B) Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company?
C	C) Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
D	D) Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
E	E) Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
F	F) Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds)
G	G) Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
H	H) Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier?
I	I) Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers?
J	J) Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication?

Table 4. Reviewer's Disclosure Information

Reviewer Number	Name of Reviewer	Disclosure Available via AAOS Disclosure System	A	B	C	D	E	F	G	H	I	J
1	Seth Sherman	Yes										
2	Alberto Gobbi	No	No	No	No	No	No	No	No	No	No	No
3	Matthew Abdel	Yes										
4	Aidin Eslam Pour	Yes										
5	Jorge Chahla	Yes										

Reviewer Responses to Structured Review Form Questions

All reviewers are asked 15 structured review questions which have been adapted from the Appraisal of Guidelines for Research and Evaluation (AGREE) II Criteria*. Their responses to these questions are listed on the next few pages.

Table 5. Reviewer Responses to Structured Review Questions 1-4

Reviewer Number	Name of Reviewer	1. The overall objective(s) of the technology overview is (are) specifically described.	2. The research covered by the technology overview is (are) specifically described.	3. The technology overview's target audience is clearly described.	4. Given the nature of the topic and the data, all clinically important outcomes are considered.
1	Seth Sherman	Strongly Agree	Strongly Agree	Disagree	Strongly Agree
2	Alberto Gobbi	Neutral	Neutral	Agree	Neutral
3	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
4	Aidin Eslam Pour	Agree	Agree	Agree	Neutral
5	Jorge Chahla	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree

Table 6. Reviewer Responses to Structured Review Questions 5-8

Reviewer Number	Name of Reviewer	5. The patients to whom this technology overview is meant to apply are specifically described.	6. The criteria used to select articles for inclusion are appropriate.	7. The reasons why some studies were excluded are clearly described.	8. All important studies that met the article inclusion criteria are included.
1	Seth Sherman	Strongly Agree	Agree	Strongly Agree	Strongly Agree
2	Alberto Gobbi	Neutral	Neutral	Neutral	Neutral
3	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
4	Aidin Eslam Pour	Neutral	Agree	Agree	Agree
5	Jorge Chahla	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree

Table 7. Reviewer Responses to Structured Review Questions 9-12

Reviewer Number	Name of Reviewer	9. The validity of the studies is appropriately appraised.	10. The methods are described in such a way as to be reproducible.	11. The statistical methods are appropriate to the material and the objectives of this technology overview.	12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed.
1	Seth Sherman	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
2	Alberto Gobbi	Agree	Agree	Agree	Neutral
3	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
4	Aidin Eslam Pour	Agree	Agree	Agree	Agree
5	Jorge Chahla	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree

Table 8. Reviewer Responses to Structured Review Questions 13-15

Reviewer Number	Name of Reviewer	13. Health benefits, side effects, and risks are adequately addressed.	14. Areas for future research are adequately addressed.	15. The writing style is appropriate for health care professionals.
1	Seth Sherman	Strongly Agree		Strongly Agree
2	Alberto Gobbi	Agree	Agree	Strongly Agree
3	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree
4	Aidin Eslam Pour	Agree	Neutral	Agree
5	Jorge Chahla	Strongly Agree	Strongly Agree	Strongly Agree

Reviewers' Recommendation for use of this technology overview in Clinical Practice

Would you recommend this technology overview be used to inform clinical practice?

Reviewer Number	Name of Reviewer	Would you recommend this technology overview be used to inform clinical practice?
1	Seth Sherman	Recommend
2	Alberto Gobbi	Recommend
3	Matthew Abdel	
4	Aidin Eslam Pour	Recommend
5	Jorge Chahla	

Reviewer Detailed Responses and Editorial Suggestions

Reviewer #1, Seth Sherman, M.D

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the technology overview; The response(s) below also include all editing suggestions received from the Additional Comments section of the structured review form.
1	Seth Sherman, M.D.	American Orthopaedic Society for Sports Medicine	A. This systematic review was extensive and thorough with a clearly described and documented search strategy. The inclusion and exclusion criteria are any studies in which BMA was used for knee OA. B. One high quality study that was included in the review (Hernigou 2018) is borderline for inclusion in the current review. This study does examine the effect of BMC in patients with osteoarthritis of the knee, however, these patients had secondary osteoarthritis as a result of underlying osteonecrosis of the femur. The BMA injections were performed in a subchondral nature, rather than intra-articular. Strictly speaking, this study does meet inclusion criteria and speaks to the question posed in this overview, but the authors must be careful to demonstrate that this study is distinct in its indications and method of administration compared to the other included studies. Additionally, in line 134, the text states "…treated with BMA microfracture x1…", however, patients were actually treated with subchondral administration of BMA (not microfracture) and were compared to TKA. In lines 140-142, the limitation that should be included is that this was a different type of BMA injection, performed within subchondral bone, for patients with osteonecrosis, which is a distinct disease process. Therefore, these results may not be applicable to a broader osteoarthritis population. C. In lines 172-175, the high-quality study results (3 total studies) are reviewed. However, the text here seems to indicate that there were 4 high quality studies included. This should be clarified. D. In lines 240-242, the authors describe a potential course of future research to include applying biologics or controls to uninvolved knees. This seems unlikely to provide valuable evidence in assessing variability and I would not advocate for injecting asymptomatic knees.

			E. Overall, the technology overview here is well done and appropriately states that the literature is limited with critical suggestions for future research. F. The evidence for or against biologic therapies for knee OA continues to evolve at a rapid pace. Longitudinal evidence-based updates on the use of BMAC for knee OA along with comparison to other agents would be useful for the membership. I appreciate being involved in this process.

Workgroup Response to Reviewer #1

Dear Seth Sherman, M.D.,

Thank you for your expert review of the Concentrated Bone Marrow Aspirate Technology Overview. We will address your comments in the order that you listed them.

A. Thank you for the positive feedback.

B. Confirmed accuracy of subchondral administration statement. Added proposed edit to line 143 for suggested limitation.

C. Confirmed and corrected.

D. Thank you for your feedback. Edits have been made to this section to reflect this feedback.

E. Thank you for the positive feedback.

F. Thank you for the positive feedback.

Reviewer #2, Alberto Gobbi, M.D

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the technology overview; The response(s) below also include all editing suggestions received from the Additional Comments section of the structured review form.
1	Alberto Gobbi, M.D.	International Cartilage Regeneration & Joint Preservation Society	A. Traditional open-ended trocars are designed to collect small amounts of aspirate. Peripheral blood immediately fills the vacated space essentially diluting the BMA with each additional retraction of the syringe plunger. In order to achieve a therapeutic amount of BMA, large volumes of BMA must be collected and processed and concentrated i.e., by centrifugation, filtration or processed in a laboratory to produce a Bone Marrow Concentrate (BMC). B. There are various methods to produce a n optimized Bone Marrow Aspirate Cell Population. The most popular method is to employ the use of commercialized kits designed to be used at the "point of care" to conduct a volume reduction or concentration of BMA by removing significant portions of RBC's and Plasma from the diluted BMA. These kits demand that the BMA be processed off the sterile field and then returned following aseptic technique. Other "non-point of care" methods require cell optimization in a laboratory employing gradient separation i.e. Ficol, followed by cultivation steps. These methods are not point of care, requiring additional surgical interventions. Newer systems are now coming of age focusing on preferential BMA collection by preventing vast amounts of peripheral blood from contaminating the BMA. These systems collect BMA via a closed tip trocar with side fenestrations forcing BMA collection preferentially laterally mitigating dilution and centrifugation requirements. The Optimized BMA never leaves the sterile field while achieving the cellular characteristics expected via centrifugation. C. Aspiration is typically collected prior to the surgical intervention to allow time for off field preparation. Aspiration only takes a few 198- 203 minutes. However, the concentration processing must be done outside of the sterile field and can take on the order of 15-30 minutes. Companies specializing in this 199-204 industry provide a centrifuge and special sterile equipment in order to concentrate the bone marrow. Optimized BMA via Closed Tip Lateral Aspiration can be collected as deemed appropriate and does not require additional

steps in the surgical intervention. The Optimized BMA can be collected on demand to meet volume and guidelines. The Optimized BMA never leaves the sterile field providing additional security and freshness. 200-205

D. At O.A.S.I bioresearch foundation we have experience of Prospective trial of BMAC vs MACI for full thickness cartilage using HYAFF11 scaffold . (1) 37 patients with full thickness patellofemoral chondral lesions 3 year follow up, 19 MACI 18 BMAC. Follow up was done with clinical scores. In 6 of BMAC and 5 of MACI patients a second look could be done. We had a significative improvement from baseline characteristics in both groups, but no significant difference between the two groups. MRI showed a complete filling of defect I 76% of MACI and 81% in BMAC. Microfracture v/s BMAC using hyaluronic acid Scaffold. 5 years follow up. Patients. full thicknes chondral lesion. with either one of the techniques. Both treatment groups achieved significant improvement at 2 years, but the BMAC group 100% had normal or nearly normal IKDC scores versus 64% in the microfracture group. At 5 years Lysholm and IKDC subjective scores were similar between the two treatment groups.

The importance of this other studies are:

- BMAC is not only intended by injection application.
- Studies regarding BMAC are not so many, so they should be taken in count in order to gain a more holistic approach to BMAC effects.
- These techniques are still in development, there exist a lack of official protocols which make the different studies difficult to compare.
- The number of participants is limited because of Hight costs, and limited background.
- Is important that the conclusions have to be taken with caution, they should give us a path to follow (or not to follow) rather than closing doors. we have still much more to learn and improve.

E. The construction and analysis are quite well done but the underlying concept of analyzing these publications that are completely independent of another is like comparing apples and pecans. Both grow on trees but have very little to do with each other.

F. Additionally, utilization of BMC for “Bone Marrow Concentrate” is also a misnomer in my opinion. The cellular composition of Harvest, Biomet,

			Arteriocyte and EMCYTE, etc… bear very few common attributes with one another. BMC should actually be attributed to "Bone Marrow Cells" The actual cellular characterization of that BMC sample should be determinant of the biologic versus whether it was obtained via centrifugation or selective aspiration i.e. Marrow Cellution. G. Much of the same can be said for the PRP comparisons concluded in the article. As we all know, PRP is not PRP! The actual cell attributes are much more critical when drawing conclusions from a study using i.e. EMCYTE vs RegenLab for instance. The intercellular make up i.e. PLT Yield, RBC Content, MON/NEU ratios must be much more deeply analyzed to draw conclusions. For example, CENTENO will not divulge how he prepares his PRP nor its characteristics.

Workgroup Response to Reviewer #2

Dear Alberto Gobbi, M.D.,

Thank you for your expert review of the Concentrated Bone Marrow Aspirate Technology Overview. We will address your comments in the order that you listed them.

A. Thank you for your feedback.

B. Thank you for your feedback.

C. Thank you for your feedback.

D. No comment.

E. Thank you for your positive feedback.

F. No comment.

G. No comment.

Reviewer #3, Matthew Abdel, M.D

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the technology overview; The response(s) below also include all editing suggestions received from the Additional Comments section of the structured review form.
1	Matthew Abdel, M.D.	Board of Directors, American Academy of Orthopaedic Surgeons	A. Excellent summary of placebo-based and non-placebo based world-wide investigation of BMA. Well written, well summarized, and scientifically excellent.

Workgroup Response to Reviewer #3

Dear Matthew Abdel, M.D.,

Thank you for your expert review of the Concentrated Bone Marrow Aspirate Technology Overview. We will address your comments in the order that you listed them.

A. Thank you for the positive feedback.

Reviewer #4, Aidin Eslam Pour, M.D

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the technology overview; The response(s) below also include all editing suggestions received from the Additional Comments section of the structured review form.
1	Aidin Eslam Pour, M.D.	American Association of Hip and Knee Surgeons	A. The team has done a great job doing the literature search and summarizing the results and writing the paper. I do not have much to add to the draft. I do not think there is strong evidence regarding the benefits of the use of bone marrow aspirate in clinical setting at this time.

Workgroup Response to Reviewer #4

Dear Aidin Eslam Pour, M.D.,

Thank you for your expert review of the Concentrated Bone Marrow Aspirate Technology Overview. We will address your comments in the order that you listed them.

A. Thank you for the positive feedback.

Reviewer #5, Jorge Chahla, M.D

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the technology overview; The response(s) below also include all editing suggestions received from the Additional Comments section of the structured review form.
1	Jorge Chahla, M.D.	Arthroscopy Association of North America	A. It is a well-performed literature search and summary of the available data on BMAC which is not extensive. It provides a clear framework for clinicians to guide decision-making concerning BMAC utilization for the treatment of symptomatic osteoarthritis.

Workgroup Response to Reviewer #5

Dear Jorge Chahla, M.D.,

Thank you for your expert review of the Concentrated Bone Marrow Aspirate Technology Overview. We will address your comments in the order that you listed them.

A. Thank you for the positive feedback.

Appendix A – Structured Review Form

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1. The overall objective(s) of the technology overview is (are) specifically described.	○	○	○	○	○
2. The research covered by the technology overview is (are) specifically described.	○	○	○	○	○
3. The technology overview's target audience is clearly described.	○	○	○	○	○
4. Given the nature of the topic and the data, all clinically important outcomes are considered.	○	○	○	○	○
5. The patients to whom this technology overview is meant to apply are specifically described.	○	○	○	○	○
6. The criteria used to select articles for inclusion are appropriate.	○	○	○	○	○
7. The reasons why some studies were excluded are clearly described.	○	○	○	○	○
8. All important studies that met the article inclusion criteria are included.	○	○	○	○	○
9. The validity of the studies is appropriately appraised.	○	○	○	○	○
10. The methods are described in such a way as to be reproducible.	○	○	○	○	○
11. The statistical methods are appropriate to the material and the objectives of this technology overview.	○	○	○	○	○
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed.	○	○	○	○	○
13. Health benefits, side effects, and risks are adequately addressed.	○	○	○	○	○
14. Areas for future research are adequately addressed.	○	○	○	○	○
15. The writing style is appropriate for health care professionals.	○	○	○	○	○

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the draft:

Would you recommend this technology overview be used to inform clinical practice? (REQUIRED)

- ○ Strongly Recommend
- ○ Recommend
- ○ Would Not Recommend
- ○ Unsure

Additional Comments regarding this technology overview?