



FEP Medical Policy Manual

FEP 8.01.55 Stem Cell Therapy for Peripheral Arterial Disease

Annual Effective Policy Date: April 1, 2026

Original Policy Date: March 2013

Related Policies:

8.01.52 - Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Stem Cell Therapy for Peripheral Arterial Disease

Description

Description

Peripheral arterial disease (PAD) is a common atherosclerotic syndrome associated with significant morbidity and mortality. Critical limb ischemia (CLI) is the end stage of lower-extremity PAD in which severe obstruction of blood flow results in ischemic pain at rest, ulcers, and a significant risk for limb loss. Use of autologous stem cells freshly harvested and allogeneic stem cells are reported to have a role in the treatment of PAD.

OBJECTIVE

The objective of this evidence review is to evaluate whether stem cell therapy improves the net health outcome in patients with peripheral arterial disease.

POLICY STATEMENT

Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of stem cells from concentrated bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source, is considered **investigational**.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Several point-of-care concentrations of bone marrow aspirate have been cleared by the FDA through the 510(k) process and are summarized in Table 1.

Table 1. FDA Approved Point-of-Care Concentration of Bone Marrow Aspirate Devices

Device	Manufacturer	Location	Date Cleared	510(k) No.
The SmartPrep Bone Marrow Aspirate Concentrate System, SmartPrep Platelet Concentration System	Harvest Technologies (now MD Biologix)	Lakewood, CO	12/06/2010	K103340
MarrowStim Concentration System (MSC system)	Biomet Biologics, Inc (now Zimmer Biomet)	Warsaw, IN	12/18/2009	BK090008
PureBMC SupraPhysiologic Concentrating System	EmCyte Corporation	Fort Myers, Florida	5/30/2019	K183205
Arthrex Angel System Kit	Arthrex, Inc.	Naples, Florida	5/23/2018	BK180180
Magellan Autologous Platelet Separator System	Arteriocyte Medical Systems (Medtronic)	Memphis, TN	11/09/2004	BK040068
BioCUE Platelet Concentration Kit (now BioCUE Blood and Bone Marrow Aspiration (bBMA) Concentration Kit)	Biomet Biologics, Inc. (now Zimmer Biomet)	Warsaw, IN	5/26/2010	BK100027
ART BMC/ART BMC PLUS System	SpineSmith Holdings, LLC (now Ceiling Biosciences)	Austin, TX	Not available	Not available
PXP System (now PXP-1000)	ThermoGenesis Corp.	Rancho Cordova, CA	07/10/2008	K081345

U.S. Food and Drug Administration product code: JQC.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

RATIONALE

Summary of Evidence

For individuals who have peripheral arterial disease (PAD) who receive stem cell therapy, the evidence includes small randomized trials and systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. The current literature on stem cells as a treatment for critical limb ischemia (CLI) due to PAD consists primarily of phase 2 studies using various cell preparation methods and methods of administration. A meta-analysis of the trials with the lowest risk of bias has shown no significant benefit of stem cell therapy for overall survival, amputation-free survival, or amputation rates. Three randomized controlled trials (RCTs) have been published that used granulocyte-macrophage colony-stimulating factor (GM-CSF)-mobilized peripheral blood mononuclear cells (PBMNC). The route of administration of cell therapy and the primary outcomes differed between studies. In the trial that added cell therapy to guideline-based care, there were no significant differences in progression-free survival and frequency of limb amputation at 1 year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms. Well-designed RCTs with a larger number of subjects and low risk of bias are needed to evaluate the health outcomes of these various procedures. Several are in progress, including multicenter randomized, double-blind, placebo-controlled trials. More data on the safety and durability of these treatments are also needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in "Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association and the American College of Cardiology

In 2016, the guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) provided recommendations on the management of patients with lower-extremity peripheral arterial disease (PAD), including surgical and endovascular revascularization for critical limb ischemia.^{25,26} Stem cell therapy for PAD was not addressed.

In 2024, the ACC/AHA along with other national organizations published updated guidance for the management of lower extremity PAD.²⁷ Stem cell therapy for PAD was not addressed.

European Society of Cardiology

In 2011, the European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of PAD did not recommend for or against stem cell therapy for PAD.²⁸ However, in 2017, updated guidelines, published in collaboration with the European Society of Vascular Surgery, stated: "Angiogenic gene and stem cell therapy are still being investigated with insufficient evidence in favour of these treatments." The current recommendation is that stem cell/gene therapy is not indicated in patients with chronic limb-threatening ischemia (class of recommendation: III; Level of evidence: B).²⁹ In 2024, recommendations for PAD and aortic diseases were updated and consolidated into one guideline.³⁰ Stem cell therapy was not addressed.

Global Vascular Guideline

In 2019, a Global Vascular Guideline on management of chronic limb-threatening ischemia summarized the available literature on therapeutic angiogenesis for various etiologies.³¹ The guideline was a joint venture of the Society for Vascular Surgery, the European Society for Vascular Surgery, and the World Federation of Vascular Societies. Based on a moderate level of evidence, the guideline recommended that therapeutic

angiogenesis in patients with chronic limb-threatening ischemia should be limited to the context of a clinical trial (strong recommendation). The authors noted that Phase 3 clinical trials are planned or underway so additional data may be forthcoming in the future.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Kullo IJ, Rooke TW. CLINICAL PRACTICE. Peripheral Artery Disease. *N Engl J Med*. Mar 03 2016; 374(9): 861-71. PMID 26962905
2. Liew NC, Lee L, Nor Hanipah Z, et al. Pathogenesis and Management of Buerger's Disease. *Int J Low Extrem Wounds*. Sep 2015; 14(3): 231-5. PMID 26264874
3. Krishna SM, Moxon JV, Golledge J. A review of the pathophysiology and potential biomarkers for peripheral artery disease. *Int J Mol Sci*. May 18 2015; 16(5): 11294-322. PMID 25993296
4. Hussain MA, Al-Omran M, Creager MA, et al. Antithrombotic Therapy for Peripheral Artery Disease: Recent Advances. *J Am Coll Cardiol*. May 29 2018; 71(21): 2450-2467. PMID 29793635
5. Rigato M, Monami M, Fadini GP. Autologous Cell Therapy for Peripheral Arterial Disease: Systematic Review and Meta-Analysis of Randomized, Nonrandomized, and Noncontrolled Studies. *Circ Res*. Apr 14 2017; 120(8): 1326-1340. PMID 28096194
6. Xie B, Luo H, Zhang Y, et al. Autologous Stem Cell Therapy in Critical Limb Ischemia: A Meta-Analysis of Randomized Controlled Trials. *Stem Cells Int*. 2018; 2018: 7528464. PMID 29977308
7. Gao W, Chen D, Liu G, et al. Autologous stem cell therapy for peripheral arterial disease: a systematic review and meta-analysis of randomized controlled trials. *Stem Cell Res Ther*. May 21 2019; 10(1): 140. PMID 31113463
8. Pu H, Huang Q, Zhang X, et al. A meta-analysis of randomized controlled trials on therapeutic efficacy and safety of autologous cell therapy for atherosclerosis obliterans. *J Vasc Surg*. Apr 2022; 75(4): 1440-1449.e5. PMID 34788653
9. Moazzami B, Mohammadpour Z, Zabala ZE, et al. Local intramuscular transplantation of autologous bone marrow mononuclear cells for critical lower limb ischaemia. *Cochrane Database Syst Rev*. Jul 08 2022; 7(7): CD008347. PMID 35802393
10. Prochzka V, Gumulec J, Jalůvka F, et al. Cell therapy, a new standard in management of chronic critical limb ischemia and foot ulcer. *Cell Transplant*. 2010; 19(11): 1413-24. PMID 20529449
11. Benoit E, O'Donnell TF, Iafrati MD, et al. The role of amputation as an outcome measure in cellular therapy for critical limb ischemia: implications for clinical trial design. *J Transl Med*. Sep 27 2011; 9: 165. PMID 21951607
12. Skra J, Pupka A, Janczak D, et al. Combined autologous bone marrow mononuclear cell and gene therapy as the last resort for patients with critical limb ischemia. *Arch Med Sci*. Apr 25 2015; 11(2): 325-31. PMID 25995748
13. Gupta PK, Krishna M, Chullikana A, et al. Administration of Adult Human Bone Marrow-Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells in Critical Limb Ischemia Due to Buerger's Disease: Phase II Study Report Suggests Clinical Efficacy. *Stem Cells Transl Med*. Mar 2017; 6(3): 689-699. PMID 28297569
14. Dubsk M, Huskov J, Bem R, et al. Comparison of the impact of autologous cell therapy and conservative standard treatment on tissue oxygen supply and course of the diabetic foot in patients with chronic limb-threatening ischemia: A randomized controlled trial. *Front Endocrinol (Lausanne)*. 2022; 13: 888809. PMID 36105404
15. Henderson, F. C., Sarel, I., Tuchman, K., Lewis, S., & Hsiang, Y. (2024). Angiogenic Precursor Cell Treatment of Critical Limb Ischemia Decreases Ulcer Size, Amputation and Death Rate: Re-Examination of phase II ACP NO-CLI Trial Data. *Journal ISSN*, 2766, 2276.
16. Teraa M, Sprengers RW, Schutgens RE, et al. Effect of repetitive intra-arterial infusion of bone marrow mononuclear cells in patients with no-option limb ischemia: the randomized, double-blind, placebo-controlled Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial. *Circulation*. Mar 10 2015; 131(10): 851-60. PMID 25567765
17. Peeters Weem SM, Teraa M, den Ruijter HM, et al. Quality of Life After Treatment with Autologous Bone Marrow Derived Cells in No Option Severe Limb Ischemia. *Eur J Vasc Endovasc Surg*. Jan 2016; 51(1): 83-9. PMID 26511056
18. Walter DH, Krankenberg H, Balzer JO, et al. Intraarterial administration of bone marrow mononuclear cells in patients with critical limb ischemia: a randomized-start, placebo-controlled pilot trial (PROVASA). *Circ Cardiovasc Interv*. Feb 01 2011; 4(1): 26-37. PMID 21205939
19. Powell RJ, Comerota AJ, Berceci SA, et al. Interim analysis results from the RESTORE-CLI, a randomized, double-blind multicenter phase II trial comparing expanded autologous bone marrow-derived tissue repair cells and placebo in patients with critical limb ischemia. *J Vasc Surg*. Oct 2011; 54(4): 1032-41. PMID 21684715
20. Powell RJ, Marston WA, Berceci SA, et al. Cellular therapy with Ixmyelocel-T to treat critical limb ischemia: the randomized, double-blind, placebo-controlled RESTORE-CLI trial. *Mol Ther*. Jun 2012; 20(6): 1280-6. PMID 22453769

21. Norgren L, Weiss N, Nikol S, et al. PACE: randomized, controlled, multicentre, multinational, phase III study of PLX-PAD for critical limb ischaemia in patients unsuitable for revascularization: randomized clinical trial. *Br J Surg*. Jan 31 2024; 111(2). PMID 38294084
22. Poole J, Mavromatis K, Binongo JN, et al. Effect of progenitor cell mobilization with granulocyte-macrophage colony-stimulating factor in patients with peripheral artery disease: a randomized clinical trial. *JAMA*. Dec 25 2013; 310(24): 2631-9. PMID 24247554
23. McDermott MM, Ferrucci L, Tian L, et al. Effect of Granulocyte-Macrophage Colony-Stimulating Factor With or Without Supervised Exercise on Walking Performance in Patients With Peripheral Artery Disease: The PROPEL Randomized Clinical Trial. *JAMA*. Dec 05 2017; 318(21): 2089-2098. PMID 29141087
24. Horie T, Yamazaki S, Hanada S, et al. Outcome From a Randomized Controlled Clinical Trial - Improvement of Peripheral Arterial Disease by Granulocyte Colony-Stimulating Factor-Mobilized Autologous Peripheral-Blood-Mononuclear Cell Transplantation (IMPACT). *Circ J*. Jul 25 2018; 82(8): 2165-2174. PMID 29877199
25. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. Mar 21 2017; 69(11): e71-e126. PMID 27851992
26. Valentine EA, Ochroch EA. 2016 American College of Cardiology/American Heart Association Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Perioperative Implications. *J Cardiothorac Vasc Anesth*. Oct 2017; 31(5): 1543-1553. PMID 28826846
27. Gornik HL, Aronow HD, Goodney PP, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. Jun 18 2024; 83(24): 2497-2604. PMID 38752899
28. Tendera M, Aboyans V, Bartelink ML, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. Nov 2011; 32(22): 2851-906. PMID 21873417
29. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. Mar 01 2018; 39(9): 763-816. PMID 28886620
30. Mazzolai L, Teixido-Tura G, Lanzi S, et al. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J*. Sep 29 2024; 45(36): 3538-3700. PMID 39210722
31. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. Jun 2019; 69(6S): 3S-125S.e40. PMID 31159978

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2013	New policy	Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow aspirate is considered investigational.
September 2013	Replace policy	Policy updated with literature review. References 3, 4, 6, 10, 12, 13, and 15 added, Some reordered. Policy statement unchanged.
September 2014	Replace policy	Policy updated with literature review, references 5, 14 added; policy statement unchanged.
September 2015	Replace policy	Policy updated with literature review, references 4, 9, and 23 added; policy statement unchanged.
June 2018	Replace policy	Policy updated with literature review through November 7, 2017; references 3, 4, 7, 9, 14, 15 and 17 added. Policy statement unchanged.
March 2019	Replace policy	Policy updated with literature review through October 29, 2018; references 4, 8 and 16 added. Policy statement unchanged.
March 2020	Replace policy	Policy updated with literature review through November 22, 2019; references added. Policy statement unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

Date	Action	Description
March 2021	Replace policy	Policy updated with literature review through December 1, 2020; references added. Policy statement unchanged.
March 2022	Replace policy	Policy updated with literature review through October 18, 2021; no references added. Policy statement unchanged.
March 2023	Replace policy	Policy updated with literature through December 2, 2022; references added. Policy statement unchanged.
March 2024	Replace policy	Policy updated with literature review through November 10, 2023; references added. Policy statement unchanged.
March 2025	Replace policy	Policy updated with literature review through December 5, 2024; references added. Policy statement unchanged.
March 2026	Replace policy	Policy updated with literature review through November 24, 2025; reference added. Policy statement unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.