# Corporate Medical Policy

## Stem-cell Therapy for Peripheral Arterial Disease

**File Name:** stem_cell_therapy_for_peripheral_arterial_disease
**Origination:** 7/2011
**Last Review:** 10/2023

## Description of Procedure or Service

**Background**
Peripheral arterial disease (PAD) is a common atherosclerotic syndrome that is associated with significant morbidity and mortality. A less-common cause of PAD is Buerger disease, also called thromboangiitis obliterans, which is a nonatherosclerotic segmental inflammatory disease that occurs in younger patients and is associated with tobacco use. Development of PAD is characterized by narrowing and occlusion of arterial vessels and eventual reduction in distal perfusion. Critical limb ischemia 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.

Two endogenous compensating mechanisms may occur with occlusion of arterial vessels: capillary growth (angiogenesis) and development of collateral arterial vessels (arteriogenesis). Capillary growth is mediated by hypoxia-induced release of chemokines and cytokines such as vascular endothelial growth factor (VEGF), and occurs by sprouting of small endothelial tubes from pre-existing capillary beds. The resulting capillaries are small and cannot sufficiently compensate for a large occluded artery. Arteriogenesis with collateral growth is, in contrast, initiated by increasing shear forces against vessel walls when blood flow is redirected from the occluded transport artery to the small collateral branches, leading to an increase in the diameter of pre-existing collateral arterioles.

The mechanism underlying arteriogenesis includes the migration of bone marrow-derived monocytes to the perivascular space. The bone marrow-derived monocytes adhere to and invade the collateral vessel wall. It is not known if the expansion of the collateral arteriole is due to the incorporation of stem cells into the wall of the vessel or to cytokines released by monocytic bone marrow cells that induce the proliferation of resident endothelial cells. It has been proposed that bone marrow-derived monocytic cells may be the putative circulating endothelial progenitor cells. Notably, the same risk factors for advanced ischemia (diabetes, smoking, hyperlipidemia and advanced age) are also risk factors for a lower number of circulating progenitor cells.

Use of autologous stem cells freshly harvested and allogeneic stem cells are reported to have a role in the treatment of peripheral arterial disease. Stem cells can be administered in a variety of routes, derived from different progenitors, and be grouped with different co-factors, many of which are being studied in order to determine the best clinical option for patients. The primary outcome in stem cell therapy trials regulated by the U.S. Food and Drug Administration (FDA) is amputation-free survival, defined as time to major amputation and/or death from any cause. Other outcomes for critical limb ischemia include the Rutherford criteria for limb status, healing of ulcers, the Ankle-Brachial Index, transcutaneous oxygen pressure, and pain-free walking. The Ankle-Brachial Index measures arterial segmental pressures on the ankle and brachium and indexes ankle systolic pressure against brachial systolic pressure (normative range, 0.95-1.2 mm Hg).

**Regulatory Status**

Several point-of-care concentrations of bone marrow aspirate have been cleared for marketing by the FDA through the 510(k) process:

The SmartPrep® Bone Marrow Aspirate Concentrate System, SmartPrep Platelet Concentration System (Harvest Technologies, now MD Biologix)

MarrowStim™ Concentration Kit System (Biomet Biologics, Inc., now Zimmer Biomet)

PureBMC SupraPhysiologic Concentrating System (EmCyte Corporation)

Arthrex Angel® System Kit (Arthrex, Inc.)

Magellan® Autologous Platelet Separator System (Arteriocyte Medical Systems -Medtronic)

BioCUE® Platelet Concentration Kit, now BioCUE® Blood and Bone Marrow Aspiration (bBMA) Concentration Kit (Biomet Biologics, Inc., now Zimmer Biomet)

ART BMC/ART BMC PLUS System (SpineSmith Holdings, LLC, now Ceiling Biosciences)

PXP® System, now PXP®-1000 (ThermoGenesis Corp.)

**Related Policies:**
Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia
Orthopedic Applications of Stem Cell Therapy
Growth Factors in Wound Healing

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

**Stem-cell therapy for the treatment of peripheral arterial disease is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.**

## Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

## When Stem-cell Therapy for Peripheral Arterial Disease is covered

Not applicable

## When Stem-cell Therapy for Peripheral Arterial Disease is not covered

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

The evidence for stem cell therapy in individuals who have peripheral arterial disease (PAD) 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 due to PAD consists primarily of phase 2 studies using various cell preparation methods and methods of administration. Meta-analysis of these trials with the lowest risk of bias shows no significant benefit of stem cell therapy for overall survival, amputation-free survival, or amputation rates. Three randomized controlled trials have been published that use granulocyte-macrophage colony-stimulating factor (GM-CSF) mobilized peripheral blood mononuclear cells (PBMNC). The route of administration of the 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 progressive-free survival and frequency of limb amputation at one year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms.

Well-designed randomized controlled trials 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 technology results in an improvement in the net health outcome.

## Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes*: *0263T, 0264T, 0265T*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 5/12/11

National Institutes of Health (NIH). Clinical Trial NCT01245335. Bone Marrow Aspirate Concentrate (BMAC) for Treatment of Critical Limb Ischemia (CLI). Retrieved on May 23, 2011 from http://clinicaltrials.gov/show/NCT01245335

National Institutes of Health (NIH). Clinical Trial NCT00919516. Autologous Bone Marrow Mononuclear Cell Implantation for Moderate to Severe Peripheral Arterial Disease. Retrieved on May 23, 2011 from http://clinicaltrials.gov/ct2/show/NCT00919516

Medical Director review 7/2011

Specialty Matched Consultant Advisory Panel review 10/2011

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). Circulation Cardiovascular interventions 2011; 4(1):26-37. Retrieved on May 31, 2012 from http://circinterventions.ahajournals.org/content/4/1/26.long

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 5/10/12

Specialty Matched Consultant Advisory Panel review 10/2012

Powell RJ, Marston WA, Berceli SA, Guzman R, Henry TD, Longcore AT, Stern TP, Watling S, Bartel RL. Cellular therapy with Ixmyelocel-T to treat critical limb ischemia: the randomized, double-blind, placebo-controlled RESTORE-CLI trial. Mol Ther. 2012 Jun; 20(6):1280-6. doi: 10.1038/mt.2012.52. Retrieved from http://www.nature.com/mt/journal/v20/n6/full/mt201252a.html

National Institutes of Health (NIH). Clinical Trial NCT01049919. Safety and Efficacy Study of Autologous Concentrated Bone Marrow Aspirate (cBMA) for Critical Limb Ischemia (CLI). Retrieved from http://clinicaltrials.gov/ct2/show/NCT01049919?term=NCT01049919&rank=1

National Institutes of Health (NIH). Clinical Trial NCT00951210. Safety of Intramuscular Injections (IM) of Allogeneic PLX-PAD Cells for the Treatment of Critical Limb Ischemia (CLI). Retrieved from http://clinicaltrials.gov/ct2/show/NCT00951210?term=NCT00951210&rank=1

Liu FP, Dong JJ, Sun SJ et al. Autologous bone marrow stem cell transplantation in critical limb ischemia: a meta-analysis of randomized controlled trials. Chin Med J 2012; 125(23):4296-300.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 5/9/13

Specialty Matched Consultant Advisory Panel review 10/2013

Poole J, Mavromatis K, Binongo JN et al. Effect of progenitor cell mobilization with granulocytemacrophage colony-stimulating factor in patients with peripheral artery disease: a randomized clinical trial. JAMA 2013; 310(24):2631-9.

McDermott MM, Guralnik JM, Criqui MH, Ferrucci L, Zhao L, Liu K, Domanchuk K, Spring B, Tian L, Kibbe M, Liao Y, Lloyd Jones D, Rejeski WJ.

Bartel RL, Booth E, Cramer C et al. From bench to bedside: review of gene and cell-based therapies
and the slow advancement into phase 3 clinical trials, with a focus on Aastrom's Ixmyelocel-T. Stem Cell Rev 2013; 9(3):373-83.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 5/22/14

Specialty Matched Consultant Advisory Panel review 11/2014

Senior Medical Director review 11/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 5/21/15

Specialty Matched Consultant Advisory Panel review 10/2015

Senior Medical Director review 10/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 1/14/16

Specialty Matched Consultant Advisory Panel review 10/2016

Medical Director review 10/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 7/2017

Medical Director review 7/2017

Specialty Matched Consultant Advisory Panel review 10/2017

Medical Director review 10/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 2/2018

Specialty Matched Consultant Advisory Panel review 10/2018

Medical Director review 10/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 2/2018

Specialty Matched Consultant Advisory Panel review 10/2019

Medical Director review 10/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 2/2020

Specialty Matched Consultant Advisory Panel review 10/2020

Medical Director review 10/2020

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.55, 2/2021

Specialty Matched Consultant Advisory Panel review 10/2021

Medical Director review 10/2021

Specialty Matched Consultant Advisory Panel review 10/2022

Medical Director review 10/2022

## Policy Implementation/Update Information

7/19/11 New policy implemented. Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow aspirate is considered investigational. Medical Director review 7/2011. (mco)

11/8/11 Specialty Matched Consultant Advisory Panel review 10/2011.No changes to Policy Statements. (mco)

6/29/12 References updated. No changes to Policy Statement. (mco)

11/13/12 Specialty Matched Consultant Advisory Panel review 10/2012. No changes to Policy Statements. (mco)

6/11/13 Description section updated and Related Policies added. Policy Guidelines updated. References updated. No changes to Policy Statements. (mco)

11/12/13 Specialty Matched Consultant Advisory Panel review 10/2013. No changes to Policy Statements. (mco)

7/15/14 References updated. No changes to Policy Statements. (mco)

1/13/15 References updated. Related Policies added. Specialty Matched Consultant Advisory Panel review 11/2014. Senior Medical Director review 11/2014. No changes to Policy statements. (td)

7/1/15 References updated. Policy Statements remain unchanged. (td)

12/30/15 References updated. Specialty Matched Consultant Advisory Panel review 10/29/2015. Medical Director review 10/2015. (td)

4/29/16 Policy Guidelines section updated. References updated. (td)

11/22/16 Specialty Matched Consultant Advisory Panel review 10/2016. Medical Director review 10/2016. (jd)

7/28/17 Policy revised with updated language clarification under the "When Not Covered" section, to include "stem cells from concentrated bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source is considered investigational." No change to policy intent. Medical Director review 7/2017. (jd)

11/10/17 Minor revisions to Policy Guidelines. Specialty Matched Consultant Advisory Panel review 10/2017. Medical Director review 10/2017. (jd)

11/9/18 References updated. Specialty Matched Consultant Advisory Panel review 10/2018. Medical Director review 10/2018. (jd)

2/26/19 Description section and regulatory status updated. Policy guidelines updated with minor revisions and references updated. (jd)

10/29/19 Specialty Matched Consultant Advisory Panel review 10/2019. Medical Director review 10/2019. (jd)

2/25/20 Minor revisions and updates to the Description section, regulatory status, policy guidelines, and reference section. No change to policy intent. (jd)

11/10/20 Specialty Matched Consultant Advisory Panel review 10/2020. Medical Director review 10/2020. (jd)

11/2/21 Description section and references updated. Specialty Matched Consultant Advisory Panel review 10/2012. Medical Director review 10/2021. (jd)

11/1/22 References updated. Specialty Matched Consultant Advisory Panel review 10/2022. Medical Director review 10/2022. (tm)

11/7/23 Description section, Regulatory Status, Policy Guidelines and References updated. Specialty Matched Consultant Advisory Panel review 10/2023. Medical Director review 10/2023. (tm)