

## MEDICAL POLICY

POLICY TITLE	STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE
POLICY NUMBER	MP 2.089

CLINICAL BENEFIT	<input checked="" type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	4/1/2025

[POLICY RATIONALE](#)  
[DISCLAIMER](#)  
[POLICY HISTORY](#)

[PRODUCT VARIATIONS](#)  
[DEFINITIONS](#)  
[CODING INFORMATION](#)

[DESCRIPTION/BACKGROUND](#)  
[BENEFIT VARIATIONS](#)  
[REFERENCES](#)

### I. POLICY

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** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

***Cross-Reference:***

**MP 2.033 Recombinant and Autologous Platelet Derived Growth Factors as Treatment of Wound Healing and Other Non-Orthopedic Conditions**  
**MP 2.080 Orthopedic Applications of Stem Cell Therapy Including Allograft and Bone Substitute Products used with Autologous Bone Marrow**

### II. PRODUCT VARIATIONS

[TOP](#)

This policy is only applicable to certain programs and products administered by Capital Blue Cross. Please see additional information below, and subject to benefit variations as discussed in Section VI below.

**FEP PPO** - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

### III. DESCRIPTION/BACKGROUND

[TOP](#)

#### Peripheral Arterial Disease

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE</b>
<b>POLICY NUMBER</b>	<b>MP 2.089</b>

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 thromboangitis obliterans), which is a nonatherosclerotic segmental inflammatory disease that occurs in younger patients and is associated with tobacco use. The 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.

### Physiology

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.

### Treatment

Use of autologous stem cells freshly harvested and allogeneic stem cells are reported to have a role in the treatment of PAD. 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 (ABI), transcutaneous oxygen pressure, and pain-free walking. The ABI measures arterial segmental pressures on the ankle and brachium and indexes ankle systolic pressure against brachial systolic pressure (normative range, 0.95 to 1.2 mm Hg).

### Regulatory Status

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE</b>
<b>POLICY NUMBER</b>	<b>MP 2.089</b>

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**

<b>Device</b>	<b>Manufacturer</b>	<b>Location</b>	<b>Date Cleared</b>	<b>510(k) No.</b>
<b>The SmartPrep® Bone Marrow Aspirate Concentrate System, SmartPrep Platelet Concentration System</b>	Harvest Technologies (now MD Biologix)	Lakewood, CO	12/06/2010	K103340
<b>MarrowStim Concentration System (MSC system)</b>	Biomet Biologics, Inc. (now Zimmer Biomet)	Warsaw, IN	12/18/2009	BK090008
<b>PureBMC SupraPhysiologic Concentrating System</b>	EmCyte Corporation®	Fort Myers, Florida	5/30/2019	K183205
<b>Arthrex Angel® System Kit</b>	Arthrex, Inc.	Naples, Florida	5/23/2018	BK180180
<b>Magellan® Autologous Platelet Separator System</b>	Arteriocyte Medical Systems (Medtronic)	Memphis, TN	11/09/2004	BK040068
<b>BioCUE® Platelet Concentration Kit (now BioCUE® Blood and Bone Marrow Aspiration (bBMA) Concentration kit)</b>	Biomet Biologics, Inc. (now Zimmer Biomet)	Warsaw, IN	5/26/2010	BK1000027
<b>ART BMC/ART BMC PLUS System</b>	SpineSmith Holdings, LLC (now Ceiling Biosciences)	Austin, TX	Not available	Not available
<b>PXP® System (now PXP®-1000)</b>	ThermoGenesis Corp.	Rancho Cordova, CA	07/10/2008	K081345

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

#### IV. RATIONALE

[TOP](#)

#### SUMMARY OF EVIDENCE

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE</b>
<b>POLICY NUMBER</b>	<b>MP 2.089</b>

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 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 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.

### V. DEFINITIONS

N/A

[TOP](#)

### VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

[TOP](#)

### VII. DISCLAIMER

*Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

[TOP](#)

## MEDICAL POLICY

POLICY TITLE	STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE
POLICY NUMBER	MP 2.089

### VIII. CODING INFORMATION

[TOP](#)

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Investigational; therefore, not covered:**

Procedure Codes							
0263T	0264T	0265T					

### IX. REFERENCES

[TOP](#)

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## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE</b>
<b>POLICY NUMBER</b>	<b>MP 2.089</b>

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## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE</b>
<b>POLICY NUMBER</b>	<b>MP 2.089</b>

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30. Blue Cross Blue Shield Association Medical Policy Reference Manual 8.01.55, Stem Cell Therapy for Peripheral Arterial Disease, February 2024

### X. POLICY HISTORY

[TOP](#)

<b>MP 2.089</b>	<b>07/10/2020 Consensus Review.</b> Policy statement unchanged. FEP statement updated. Benefit Variation statement updated. Product Variation Statement updated. Coding checked no changes. References reviewed, updated.
	<b>02/10/2021 Consensus Review.</b> Policy statement unchanged. Background, rationale, and references updated. Coding reviewed.
	<b>03/04/2022 Consensus Review.</b> Policy statement unchanged. Background, FEP, and references updated. No coding changes.
	<b>01/26/2023 Consensus Review.</b> Background and references updated. No changes to coding.
	<b>02/15/2024 Consensus Review.</b> Updated Regulatory status and references. No

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<b>POLICY TITLE</b>	<b>STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE</b>
<b>POLICY NUMBER</b>	<b>MP 2.089</b>

	changes to coding.
	<b>01/09/2025 Consensus Review.</b> Editorial refinements to statement; intent unchanged.

[Top](#)

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