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## MEDICAL POLICY – 8.01.55 Stem Cell Therapy for Peripheral Arterial Disease

BCBSA Ref. Policy:	8.01.55		
Effective Date:	Apr. 1, 2025	RELATED I	MEDICAL POLICIES:
Last Revised:	Mar. 10, 2025	2.01.543	Recombinant and Autologous Platelet-Derived Growth Factors for
Replaces:	N/A		Wound Healing and Other Non-Orthopedic Conditions
		8.01.52	Orthopedic Applications of Stem Cell Therapy (Including Allografts and
			Bone Substitutes Used with Autologous Bone Marrow)

## Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION EVIDENCE REVIEW | REFERENCES | HISTORY

Clicking this icon returns you to the hyperlinks menu above.

## Introduction

Peripheral arterial disease (PAD) is a condition in which plaque builds up in the arteries. Fat, cholesterol, and other substances in the blood make up the plaque. Over time the plaque becomes so thick and hard that the blood has trouble flowing through the artery. While PAD can affect the arms, organs, or the legs, it most often affects the legs. Pain and numbness are symptoms of PAD in the legs. PAD also increases the risk of infection and tissue death. If enough tissue dies, the leg may need to be removed. Using stem cells as a way to treat PAD is being studied. The idea is to use stem cells to stimulate the body to create new blood vessels. Using stem cells to treat PAD is unproven. Larger and longer studies are needed to find out if this treatment is safe and how long it might last.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

### Policy Coverage Criteria

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

## Coding

Code	Description
СРТ	
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy

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## **Related Information**

N/A

## **Evidence Review**



## 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.

## Background

### **Peripheral Arterial Disease**

PAD is a common atherosclerotic syndrome associated with significant morbidity and mortality.<sup>1</sup> A less common cause of PAD is Buerger disease (also called thromboangiitis obliterans), which is a nonatherosclerotic segmental inflammatory disease that occurs in younger individuals and is associated with tobacco use.<sup>2</sup> 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).<sup>3</sup> Capillary growth is mediated by hypoxia-induced release of chemokines and cytokines such as vascular endothelial growth factor and occurs by sprouting of small endothelial tubes from preexisting 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 preexisting 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, 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 purported to have a role in the treatment of PAD.<sup>4</sup> 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 US 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 (TcO2), 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, 0.95-1.2 mm Hg).

### **Summary of Evidence**

For individuals who have PAD who receive stem cell therapy, the evidence includes small randomized trials and systematic reviews. The relevant outcomes are overall survival, symptoms, change in disease status, morbid events, functional outcomes, guality of life, and treatmentrelated 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 colonystimulating factor (GM-CSF)-mobilized peripheral 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 progression-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 the technology results in an improvement in the net health outcome.

## **Ongoing and Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 1**.

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			, 
NCT03304821	Granulocyte-Macrophage Stimulating Factor (GM-CSF) in Peripheral Artery Disease: the GPAD-3 Study	176	Dec 2025
NCT02685098	A Clinical and Histological Analysis of Mesenchymal Stem Cells in Amputation (CHAMP)	81	Oct 2024
NCT02805023ª	Phase 1/2, Double Blind Randomized Placebo Controlled Study to Assess the Safety and Efficacy of BGC101 (EnEPC) in the Treatment of PAD & CLI	50	Dec 2027
NCT04466007	Multicenter, Randomized, Dose-search, Parallel, Double-blind, and Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of Intramuscular Administration of Allogeneic Adipose Tissue Adult Mesenchymal Stem Cells in Diabetic Patients With Critical Limb Ischemia Without Possibility of Revascularization	90	Apr 2025
Unpublished			
NCT02551679ª	A Randomized Double Blind Placebo Controlled Clinical Study to Assess Blood-Derived Autologous Angiogenic Cell Precursor Therapy in Patients With Critical Limb Ischemia (ACP-CLI)	95	Dec 2020
NCT02538978ª	Safety and Effectiveness of the SurgWerksTM-CLI Kit and VXPTM System for the Rapid Intra-operative Aspiration, Preparation and Intramuscular Injection of Concentrated Autologous Bone Marrow Cells Into the	224	Mar 2019

## Table 1. Summary of Key Trials



NCT No.	Trial Name	Planned	Completion
		Enrollment	Date
	Ischemic Index Limb of Rutherford Category 5 Non-		
	Reconstructable Critical Limb Ischemia Patients		
NCT01679990ª	A Phase II, Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled, Parallel- Groups Study to Evaluate the Safety and Efficacy of Intramuscular Injections of Allogeneic PLX-PAD Cells for the Treatment of Subjects With Intermittent Claudication (IC)	180	Feb 2019
NCT03042572	Allogeneic Mesenchymal Stromal Cells for Angiogenesis and Neovascularization in No-option Ischemic Limbs; A Double-blind, Randomized, Placebo-controlled Trial	60	July 2021

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

### **Practice Guidelines and Position Statements**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion 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 American College of Cardiology

In 2016, the guidelines from the American Heart Association and American College of Cardiology provided recommendations on the management of patients with lower-extremity PAD, including surgical and endovascular revascularization for critical limb ischemia (CLI).<sup>26,27</sup> 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.<sup>28,</sup> Stem cell therapy for PAD was not addressed.

## European Society of Cardiology

In 2011, the European Society of Cardiology guidelines on the diagnosis and treatment of PAD did not recommend for or against stem cell therapy for PAD.<sup>29</sup> 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 individuals with chronic limb-threatening ischemia (class of recommendation: III; level of evidence: B).<sup>30</sup> In 2024, recommendations for PAD and aortic diseases were updated and consolidated into one guideline.<sup>31</sup> 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.<sup>32</sup> 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 individuals 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.

## Medicare National Coverage

There is no national coverage determination.

## **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 2.

# Table 2. FDA Approved Point-of-Care Concertation of Bone MarrowAspirate Devices

Device	Manufacturer	Location	Date	510(k)
			Cleared	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	BK1000027
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

US Food and Drug Administration product code: JQC.

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# History

Date	Comments
08/09/11	New policy; add to Therapy section. Policy created with literature review through March 2011; considered investigational.
07/20/12	Replace policy. Policy updated with literature review through February 2012, rationale section revised. References 4 and 10 added. Policy statement is unchanged.
10/09/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
07/08/13	Replace policy. Policy updated with literature review through April 8, 2013; references 3, 4, 6, 10, 12, 13, 15 added; references reordered; policy statement unchanged.
08/20/13	Update Related Policies. Change title to 2.02.18.
07/31/14	Annual Review. Policy updated with literature review through April, 2014. References 5,14 added; others renumbered/removed. Policy statement unchanged.
07/14/15	Annual Review. Policy updated with literature review through April 14, 2015; references 4, 9, and 23 added; policy statement unchanged. ICD-9 and ICD-10 procedure codes removed; these were listed for informational purposes only.
04/01/16	Annual Review, approved March 8, 2016. Policy updated with literature review through November 17, 2015; references 4, 7, and 9 added; some references removed. Policy statement unchanged.
09/01/17	Annual Review, approved August 22, 2017. Policy updated with literature review through June 4, 2017; references 3 and 14 added. Policy statement updated to describe specific sources of stem cells.
05/01/18	Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references 15 and 17 added. Policy statement unchanged.
05/01/19	Annual Review, approved April 2, 2019. Policy updated with literature review through October 2018; references 4, 8 and 16 added. Policy statement unchanged.
04/01/20	Annual Review, approved March 19, 2020. Policy updated with literature review through November 2019; references added. Policy statement unchanged. Added CPT codes 20999 and 38241.
04/01/21	Annual Review, approved March 2, 2021. Policy updated with literature review through December 1, 2020; references added. Policy statement unchanged.
04/01/22	Annual Review, approved March 21, 2022. Policy updated with literature review through October 18, 2021; no references added. Policy statement unchanged. Removed CPT codes 20999 and 38241.



Date	Comments
04/01/23	Annual Review, approved March 20, 2023. Policy updated with literature through
	December 2, 2022; references added. Policy statement unchanged. Changed the
	wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Annual Review, approved March 25, 2024. Policy updated with literature review
	through November 10, 2023; references added. Policy statement unchanged.
08/01/24	Minor update to Related Policies, 2.02.18 Progenitor Cell Therapy for the Treatment of
	Damaged Myocardium Due to Ischemia was archived effective August 1, 2024.
01/01/25	Minor update to related policy. 2.01.16 was replaced with 2.01.543 Recombinant and
	Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-
	Orthopedic Conditions.
04/01/25	Annual Review, approved March 10, 2025. Policy updated with literature review
	through December 5, 2024; references added. Policy statement unchanged.

**Disclaimer**: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.