Stem Cell Therapy for Peripheral Arterial Disease

Policy # 00298
Original Effective Date: 06/15/2011
Current Effective Date: 07/12/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Recombinant and Autologous Platelet Derived Growth Factors for Wound Healing and Other Non Orthopedic Conditions is addressed separately in medical policy 00262.

Note: Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia is addressed separately in medical policy 00486.

Note: Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow) is addressed separately in medical policy 00258.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the treatment of peripheral arterial disease (PAD), 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 to be **investigational.***

Background/Overview

Peripheral Arterial Disease

PAD is a common atherosclerotic syndrome associated with significant morbidity and mortality. A less common cause of PAD is Buerger disease (also called thromboangiitis obliterans), which is a non atherosclerotic 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.

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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 the 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 reported to have a role in the treatment of peripheral arterial disease. Stems cell 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 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).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Six point-of-care concentrations of bone marrow aspirate have been cleared by the FDA through the 510(k) process and 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 SmarktPReP2®‡ Bone Marrow Aspirate Concentrate System, SmarktPReP Platelet Concentration System	Harvest Technologies	Lakewood, CO	12/06/2010	K103340
MarrowStim Concentration System (MSC system)	Biomet Biologics, Inc	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	Biomet Biologics, Inc.	Warsaw, IN	5/26/2010	BK1000027
ART BMC System	SpineSmith Holdings, LLC	Austin, TX	Not available	Not available
PXP®‡ System	ThermoGenesis Corp.	Rancho Cordova, CA	07/10/2008	K081345

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

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Rationale/Source

Peripheral arterial disease 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.

Summary of Evidence

For individuals who have 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.

Supplemental Information

Practice Guidelines and Position Statements

American Heart Association and the American College of Cardiology

In 2016, the guidelines from the American Heart Association and the American College of Cardiology provided recommendations on the management of patients with lower-extremity PAD,

including surgical and endovascular revascularization for critical limb ischemia. Stem cell therapy for PAD 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. 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.

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. 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).

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.

Ongoing and Unpublished Clinical Trials

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03968198	Autologous Transplantation of Adipose Tissue Derived Mesenchymal Stroma/Stem Cells (ASC) in Patients With Critical Limb Ischemia	43	July 2023
NCT03042572	Allogeneic Mesenchymal Stromal Cells for Angiogenesis and Neovascularization in No-option Ischemic Limbs; A Double-blind, Randomized, Placebo-controlled Trial	60	July 2021
NCT01049919[a]	MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia (CLI) in Subjects With Severe Peripheral Arterial Disease (PAD) (MOBILE)	152	September 2020
NCT03304821	Granulocyte-Macrophage Stimulating Factor (GM-CSF) in Peripheral Artery Disease: the GPAD-3 Study	176	Jun 2022
NCT03994666	Cell Therapy in Critical Limb Ischemia by Implantation of Allogeneic Umbilical Cord-derived Mesenchymal Stem Cells	30	Dec 2021
NCT02685098	A Clinical and Histological Analysis of Mesenchymal Stem Cells in Amputation (CHAMP)	16	September 2025
NCT03809494[a]	Clinical Study of the Use of an Autologous Blood Filtration Device in the Treatment of Critical Limb Ischemia	350	January 2026
NCT02805023[a]	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	December 2022

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	June 2022
NCT02551679[a]	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	December 2020
Unpublished			
NCT01483898[a]	An Efficacy and Safety Study of Ixmyelocel-T in Patients With Critical Limb Ischemia (CLI) (REVIVE)	594	Apr 2014 (last update posted Aug 2018)
NCT01245335[a]	Pivotal Study of the Safety and Effectiveness of Autologous Bone Marrow Aspirate Concentrate (BMAC) for the Treatment of Critical Limb Ischemia Due to Peripheral Arterial Disease	97	Nov 2015
NCT01745744	Clinical Trial Phase I / II, Multicentre, Open, Randomized Study of the Use of Mesenchymal Stem Cells From Adipose Tissue (CeTMAd) as Cell Regeneration Therapy in Critical Chronic Ischemic Syndrome of Lower Limb in Nondiabetic Patients	33	July 2018

NCT00498069[a]	Feasibility Study of the Safety and Activity of Autologous Bone Marrow Aspirate Concentrate (BMAC) for the Treatment of Critical Limb Ischemia Due to Peripheral Arterial Occlusive Disease	48	Mar 2015
NCT02538978[a]	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 Ischemic Index Limb of Rutherford Category 5 Non-Reconstructable Critical Limb Ischemia Patients	224	Mar 2019 (last update posted 2016 not yet recruiting)
NCT01679990[a]	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)	172	April 2018

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

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06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. New policy.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0263T, 0264T, 0265T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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