8.01.55	Stem Cell Therapy for Peripheral Arterial Disease		
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Section:	8.0 Therapy	**Page:**	Page 1 of 16

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**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

There are specific CPT category III codes for this therapy:

- **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

These CPT codes were constructed to allow reporting of the complete procedure and harvesting by a single physician (code 0263T) or separate reporting when the cell harvesting, and therapy injections are performed by separate physicians (0264T and 0265T).

Description

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.

Related Policies

- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Six 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 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.

Rationale

Background

Peripheral Arterial Disease

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 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 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 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).

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of technology. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Stem Cell Therapy in Individuals With Peripheral Arterial Disease
Clinical Context and Therapy Purpose
The purpose of stem cell therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with peripheral arterial disease (PAD).

The question addressed in this evidence review is: Does stem cell therapy improve the net health outcome in patients with PAD?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with PAD.

Interventions
The therapy being considered is stem cell therapy. The rationale for hematopoietic cell or bone marrow-cell therapy in PAD is to induce arteriogenesis by boosting the physiologic repair processes. This requires large numbers of functionally active autologous precursor cells and, subsequently, a large quantity of bone marrow (e.g., 240 to 500 mL) or another source of stem cells.

Comparators
Comparators of interest include conservative management, rehabilitation protocols, or surgical intervention. The standard therapy for severe, limb-threatening ischemia is revascularization aiming to improve blood flow to the affected extremity. If revascularization fails or is not possible, amputation is often necessary.

Outcomes
The general outcomes of interest are overall survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity including amputation rates, improved amputation-free survival, improved wound healing, ulcer healing, and pain-free walking distance. Follow-up at 3, 6, and 12 months is of interest for stem cell therapy to monitor relevant outcomes. Longer-term follow-up is also of interest.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
At this time, the literature on stem cell therapy consists primarily of small RCTs, systematic reviews and meta-analyses.[1,2,]

Systematic Reviews
Three systematic reviews have been published (Table 2). Rigato et al (2017) published a systematic review of autologous cell therapy for PAD.[3,] The authors identified 19 RCTs (837 patients), 7 nonrandomized controlled studies (338 patients), and 41 noncontrolled studies (1177 patients). There was heterogeneity across studies in setting, underlying diseases, types and doses of cells, routes of administration, and follow-up durations. Many studies were pilot or phase 2 trials and were rated as low-quality. There was an indication of publication bias. A meta-analysis of all RCTs showed a significant reduction in amputation rates, improved amputation-free survival, and improved wound healing. However, when only the placebo-controlled trials (n=19) were analyzed the effects were no longer statistically significant, and analysis of only RCTs with low risk of bias (n=3) found no benefit of cell therapy.

In a meta-analysis of RCTs, Xie et al (2018) reviewed published evidence evaluating the safety and efficacy of autologous stem cell therapy in critical limb ischemia (CLI).[4,] Cell therapy increased the probability of angiogenesis (relative risk=5.91, confidence interval [CI]: 2.49 to 14.02, p<0.0001), ulcer healing (relative risk=1.73, CI: 1.45 to 2.06, p<0.00001), and a reduction in amputation rates (relative risk=0.59, CI: 0.46 to 0.76, p<0.0001). Compared with the control group, significant improvement in the cell therapy group was also seen in Ankle-Brachial Index (ABI) (mean difference=0.13, CI=0.11 to 0.15, p<0.00001), transcutaneous oxygen tension (mean difference=12.22, CI=5.03 to 19.41, p=0.0009), and pain-free walking distance (mean difference=144.84, CI=53.03 to 236.66, p=0.002).

Gao et al (2019) reviewed 27 RCTs and found that 1186 patients and 1280 extremities were included.[5] A majority of studies showed a high-risk of bias. Meta-analysis indicated that autologous stem cell therapy was more effective than conventional therapy on the healing rate of ulcers. There was also a significant improvement in ABI, total carbon dioxide, and pain-free walking distance while a significant reduction was shown in amputation rate and rest pain scores. However, the result presented no significant improvement in major limb salvage.

Table 2. Systematic Reviews of Trials Assessing Autologous Cell Therapy for Peripheral Arterial Disease

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Gao (2019)[5]	May 2019	27	Patients with PAD or CLI who received autologous stem cell therapy	1186	RCTs	• Pooled analysis of 27 RCTs showed a significant improvement in ABI, total carbon dioxide, and pain-free walking distance while significant reduction was showed in amputation rate and rest pain scores.
Rigato (2017)[3]	Jul 2016	67	Patients with severe intractable PAD or CLI who received autologous cell therapy	2352	RCTs, cohort	• Pooled analysis of 19 RCTs showed a reduction in amputation rates, improved amputation-free survival, and improved wound healing
Xie (2018)[4]	Jan 2018	23	Patients with PAD or CLI who received autologous stem cell therapy	1118	RCTs	• Pooled analysis of 18 studies showed a reduction in amputation rate, ulcer healing, and pain-free walking distance (n=512)

ABI: Ankle-Brachial Index; CLI: critical limb ischemia; PAD: peripheral arterial disease, RCT: randomized controlled trial.

Randomized and Nonrandomized Trials

Concentrated Bone Marrow Aspirate (Monocytes and Mesenchymal Stem Cells) Intramuscular Injection

Prochazka et al (2010) reported on a randomized study of 96 patients with CLI and foot ulcers.[6] Patient inclusion criteria were CLI as defined by an ABI score of 0.4 or less, ankle systolic pressure of 50 mm Hg or less or toe systolic pressure of 30 mm Hg or less, and failure of basic conservative and revascularization treatment (surgical or endovascular). Patients were randomized to treatment with bone marrow concentrate (n=42) or standard medical care (n=54). The primary endpoints were major limb amputation during the 120 days posttreatment, and degree of pain and function at 90- and 120-day follow-ups. At baseline, the control group compared with the treatment group had a higher proportion of patients with diabetes (98.2% versus 88.1%), hyperlipidemia (80.0% versus 54.8%), and ischemic heart disease (76.4% versus 57.1%), respectively. Additionally, the control group had a higher proportion of patients (72% versus 40%) with the University of Texas Wound Classification stage DIII (deep ulcers with osteitis). For the 42 patients in the treatment group, there was a history of 50 revascularization procedures; 46 of 54 patients in the control group had a history of revascularization procedures. All 42 patients in the bone marrow group finished 90 days of follow-up, and 37 of 54 patients in the control group finished 120 days of follow-up. Differences in lengths of follow-up for the primary outcome measure were unexplained. Five patients in the bone marrow group and 8 in the control group died of causes unrelated to the therapy during follow-up. At follow-up, the frequency of major limb amputation was 21% in patients treated with bone marrow concentrate and 44% in controls. Secondary endpoints were assessed only in those treated with bone marrow concentrate. In the treatment group with salvaged limbs, toe pressure and Toe-Brachial Index score increased from 22.66 to 25.63 mm Hg and from 0.14 to

0.17, respectively. Interpretation of results is limited by unequal baseline measures, lack of blinding, differences in lengths of follow-up, differences in losses to follow-up, and differences in follow-up measures for the 2 groups.

Benoit et al (2011) reported on a U.S. Food and Drug Administration regulated, double-blind pilot RCT of 48 patients with CLI who were randomized 2:1 to bone marrow concentrate using the SmartPReP system or to iliac crest puncture with an intramuscular injection of diluted peripheral blood.[7] At a 6-month follow-up, the differences in the percentages of amputations between the bone marrow concentrate group (29.4%) and diluted peripheral blood group (35.7%) were not statistically significant. In a subgroup analysis of patients with tissue loss at baseline (Rutherford 5), intramuscular injection of bone marrow concentrate resulted in a lower amputation rate (39.1%) than placebo (71.4%).

Intramuscular injection with a combination of bone marrow mononuclear cells (BM-MNCs) and gene therapy with a vascular endothelial growth factor plasmid were tested in a 2015 European RCT assessing 32 patients.[8] Controls in this trial were treated pharmacologically, and therefore the groups were not blinded to treatment. Several objective measures were improved in the BM-MNC group, but not in the control group. These measures included ABI scores, development of collateral vessels measured with angiography, and healing rates of ischemic ulcers. Amputations were performed in 25% of patients in the BM-MNC group and in 50% of patients in the control group.

Gupta et al (2017) evaluated the efficacy and safety of intramuscular adult human bone marrow -derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeutics Research, Bangalore, India) in a phase II prospective, open-label dose-ranging study.[9] Ninety patients were nonrandomly allocated to 3 groups: 1 million cells/kg body weight (n=36), 2 million cells/kg body weight (n=36), and standard of care (SOC; n=18). Compared with the SOC group, greater reduction in rest pain and healing of ulcers were see in the 2 million cells/kg body weight group (0.3 units per month [standard error (SE): 0.13], CI: -0.55 to -0.05, p=0.0193 and 11.0% decrease in size per month [SE: 0.05%], CI: 0.80 to 0.99, p=0.0253, respectively) and in the 1 million cells/kg body weight group (0.23 per month [SE: 0.13], CI: -0.49 to 0.03, p=0.081 and 2.0% decrease in size per month [SE: 0.06%], CI: 0.87 to 1.10, p=0.6967, respectively). Limitations of this study included the geographically and ethnically homogenous cohort and a lack of clearly defined methods for cohort selection. Additionally, patients in the cell administration groups had lower ABI values and larger ulcers indicating potential investigator bias to allocate more severe patients to the treatment groups.

Intra-Arterial Injection

The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation trial was a randomized, double-blind, placebo-controlled study (2015) from Europe.[10] This foundation-supported trial evaluated the clinical effects of repeated intra-arterial infusion of BM-MNCs in 160 patients with nonrevascularizable CLI. Patients received a repeated intra-arterial infusion of BM-MNCs or placebo (autologous peripheral blood erythrocytes) into the common femoral artery. The primary outcome measure (rate of major amputation after 6 months) did not differ significantly between groups (19% for BM-MNCs versus 13% controls). Secondary outcomes of QOL, rest pain, ABI score, and transcutaneous oxygen pressure improved to a similar extent in both groups, reinforcing the need for a placebo control in this type of trial. Results from a long-term follow-up analysis of 109 of the participants found improvements in self-reported QOL persisted for a median of 35 months in both groups, who remained blinded to treatment assignment.[11] The percentages of patients undergoing amputation also remained similar in the 2 groups (25.9% for the BM-MNC group versus 25.3% for the control group).

Results from the multicenter Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease trial (2011) were reported.[12] In this double-blind, phase 2 trial, 40 patients with CLI who were not candidates or had failed to respond to interventional or surgical procedures were randomized to intra-arterial administration of BM-MNC or placebo. The cell suspension included hematopoietic, mesenchymal and other progenitor cells. After 3 months, both groups were treated with BM-MNC in an open-label phase. Twelve patients received additional treatment with BM-MNC between 6 months and 18 months. The primary outcome measure (a significant increase in the ABI score at 3 months) was not achieved (from 0.66 at baseline to 0.75 at 3 months). Limb salvage and amputation-free survival rates differed between groups. There was a significant improvement in ulcer healing (ulcer area, 1.89 cm^2 versus 2.89 cm^2) and reduced pain at rest (an improvement on a 10-point visual analog scale score of »3 versus 0.05) following intra-arterial BM-MNC administration, respectively.

Section Summary: Concentrated Bone Marrow Aspirate (Monocytes and Mesenchymal Stem Cells)

There is preliminary evidence of benefit to the use of intramuscular concentrated bone aspirate injection outcomes in CLI patients. Randomized controlled trials and a non-randomized comparative study have been published. [7,6,8,9,] Two RCTs have been published with intra-arterial injection of concentrated bone marrow aspirate.[10,12,] The RCTs did not find support for their respective primary outcome measures; the rate of major amputation after 6 months or a significant increase in the ABI score at 3 months.

Expanded Monocytes and Mesenchymal Stem Cells

Interim and final results from the industry-sponsored phase 2, randomized, double-blind, placebo-controlled RESTORE-CLI trial, which used cultured and expanded monocytes and mesenchymal stem cells (MSCs) derived from bone marrow aspirate (ixmyelocel-T), were reported by Powell et al (2011, 2012).[13,14,] Seventy-two patients with CLI received ixmyelocel-T (n=48) or placebo with sham bone marrow aspiration (n=24) and were followed for 12 months. There was a 40% reduction in any treatment failure (due primarily to differences in doubling of total wound surface area and de novo gangrene), but no significant differences in amputation rates at 12 months.

Granulocyte-Macrophage Colony-Stimulating Factor Mobilization

Poole et al (2013) reported on the results of a phase 2, double-blind, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor (GM-CSF) in 159 patients with intermittent claudication due to PAD.[15,] Patients were treated with subcutaneous injections of GM-CSF or placebo 3 times weekly for 4 weeks. The primary outcome (peak treadmill walking time at 3 months) increased by 109 seconds (296 to 405 seconds) in the GM-CSF group and by 68 seconds (308 to 376 seconds) in the placebo group (p=0.08). Changes in the physical functioning subscale score of the 36-Item Short-Form Health Survey and distance score of the Walking Impairment Questionnaire were significantly better in patients treated with GM-CSF. However, there were no significant differences between the groups in ABI score, Walking Impairment Questionnaire distance or speed scores, claudication onset time, or 36-Item Short-Form Health Survey Mental Component or Physical Component Summary scores. The post hoc exploratory analysis found that patients with more than a 100% increase in progenitor cells (CD34-positive/CD133-positive) had a significantly greater increase in peak walking times (131 seconds) than patients who had less than a 100% increase in progenitor cells (60 seconds).

McDermott et al (2017) reported results from an RCT of 210 patients with PAD that evaluated whether GM-CSF combined with supervised treadmill exercise improves 6-minute walk distance (6MWT) compared with exercise alone and compared with GM-CSF alone and to determine whether GM-CSF alone improves 6MWT more than placebo and whether exercise improves 6MWT more than an attention control intervention.[16,] Supervised exercise consisted of treadmill exercise 3 times weekly for 6 months. Participants were randomized to 1 of 4 groups: supervised exercise + GM-CSF (exercise + GM-CSF) (n = 53), supervised exercise + placebo (exercise alone) (n = 53), attention control + GM-CSF (GM-CSF alone) (n = 53), attention control + placebo (n = 51). The attention control consisted of weekly educational lectures by clinicians for 6 months. The primary outcome was change in 6MWT distance at a 12-week follow-up, with a minimum clinically important difference of 20 meters. Ninety-three percent of patients completed a 12-week follow-up. At follow-up, exercise + GM-CSF did not significantly improve 6MWT distance more than exercise alone (*p*=0.61) or more than GM-CSF alone (Hochberg-adjusted *p* = .052). GM-CSF alone did not improve a 6MWT more than attention control + placebo (*p*=0.91). Exercise alone improved a 6MWT compared with attention control + placebo (Hochberg-adjusted *p*=0.02).

Horie et al (2018) reported results from an RCT (IMPACT: Improvement of Peripheral Arterial Disease by Granulocyte Colony-Stimulating Factor-Mobilized Autologous Peripheral-Blood-Mononuclear Cell Transplantation) of 107 patients with PAD characterized as Buerger disease that evaluated the efficacy and safety of GM-CSF-mobilized peripheral blood mononuclear cell (PBMNC) transplantation compared with SOC (Tables 3 and 4).[17,] Participants were randomized to guideline-based SOC or SOC plus intramuscular weight-based PBMNC administration. After disease progression or completion of a 1-year follow-up, 17 patients in the control group underwent cell therapy. Furthermore, 21 patients underwent revascularization after completion of the protocol treatment period or after discontinuation of the study (12 in the cell therapy group, 9 in the control group; 18 patients underwent percutaneous transluminal angioplasty, 2 had bypass surgery, and 1 had thrombectomy). Serious adverse events occurred in 20% of the cell therapy group compared with 11.3% of the control group (p=0.28). Leukopenia, alkaline phosphatase elevation, and hyperuricemia were determined to be adverse events related to GM-CSF administration. This study was limited by a small number of advanced cases (Fontaine stage IV cases (20.4%)), a high-risk group of hemodialysis patients, and a high number of patients who did not complete treatment (cell therapy group: 38.5%; control group: 50.9%).

Table 3. Key Characteristics of Randomized Controlled Trial with Intramuscular Granulocyte-Macrophage Colony-Stimulating Factor-Mobilized Peripheral Blood Mononuclear Cells for Critical Limb Ischemia

					Treatment	
Study (Year)	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Horie (2018)[17,] IMPACT	Japan	17	2009 to 2013	Patients with PAD, Fontaine classification II-IV (n=107)	Intramuscular GM-CSF, single dose of 200 μg/m² per day for 4 days (n=52)	Guideline based standard of care[1] (n=55)

GM-CSF: granulocyte-macrophage colony-stimulating factor; PAD: peripheral arterial disease.
[1] Includes the use of lipid, antihypertensive, antidiabetic, antithrombotic drugs, exercise, and prostanoids.

Table 4. Results of Randomized Controlled Trial with Intramuscular Granulocyte-Macrophage Colony-Stimulating Factor-Mobilized Peripheral Blood Mononuclear Cells for Critical Limb Ischemia

Study (Year)	PFS (95% CI)	Frequency of major limb amputation	New ulcer or gangrene	Serious AE
Horie (2018)[17,] IMPACT				
Cell Therapy group	0.42 (0.13-1.36)	6.0%	18%	20.0%
Control group	0.62 (0.28-1.36)	5.7%	15.1%	11.3%
p-value	0.07	1.00	0.80	0.28

AE: adverse events; CI: confidence intervals; PFS: progression-free survival.

The purpose of the limitations tables (see Tables 5 and 6) is to display notable limitations identified in the study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Horie (2018)[17,] IMPACT		3 - fixed dosing was used (not weight-based)			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Horie (2018)[17], IMPACT		1,2,3 - open-label trial				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Granulocyte-Macrophage Colony-Stimulating Factor Mobilization

Three RCTs have been published.[15,16,17] 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 PFS and frequency of limb amputation at 1 year of follow-up.[17] There was a substantial rate of subsequent surgical intervention in both arms.

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 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

The purpose of the remaining sections in Supplemental Information is to provide reference material regarding existing practice guidelines and position statements, U.S. Preventive Services Task Force Recommendations and Medicare National Coverage Decisions and registered, ongoing clinical trials. Inclusion in the Supplemental Information does not imply endorsement and information may not necessarily be used in formulating the evidence review conclusions.

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 and the American College of Cardiology provided recommendations on the management of patients with lower-extremity peripheral arterial disease (PAD), including surgical and endovascular revascularization for critical limb ischemia.[18,19,] 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.[20,] 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.[21,] 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).[22,]

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 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03968198	Autologous Transplantation of Adipose Tissue Derived Mesenchymal Stroma/Stem	43	July 2023

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Cells (ASC) in Patients With Critical Limb Ischemia		
NCT03304821	Granulocyte-Macrophage Stimulating Factor (GM-CSF) in Peripheral Artery Disease: the GPAD-3 Study	176	Dec 2022
NCT03994666	Cell Therapy in Critical Limb Ischemia by Implantation of Allogeneic Umbilical Cord-derived Mesenchymal Stem Cells	30	Dec 2021 (Status = Unknown)
NCT02685098	A Clinical and Histological Analysis of Mesenchymal Stem Cells in Amputation (CHAMP)	16	September 2025
			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 (Status = Recruiting; last updated December 2021; no results posted)
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)

NCT No.	Trial Name	Planned Enrollment	Completion Date
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
NCT03042572	Allogeneic Mesenchymal Stromal Cells for Angiogenesis and Neovascularization in No-option Ischemic Limbs; A Double-blind, Randomized, Placebo-controlled Trial	60	July 2021 (Status = Unknown)
NCT01049919[a]	MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia (CLI) in Subjects With Severe Peripheral Arterial Disease (PAD) (MOBILE)	153	February 2020
NCT03809494[a]	Clinical Study of the Use of an Autologous Blood Filtration Device in the Treatment of Critical Limb Ischemia	2	Nov 2020 (Terminated)

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

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/11/2013	BCBSA Medical Policy adoption
06/30/2015	Coding update
01/01/2016	Policy revision without position change
09/01/2017	Policy revision without position change
04/01/2018	Policy revision without position change
04/01/2019	Policy revision without position change
03/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2021	Annual review. No change to policy statement. Literature review updated.
04/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
Stem Cell Therapy for Peripheral Arterial Disease 8.01.55 **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**.	**Stem Cell Therapy for Peripheral Arterial Disease 8.01.55** **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**.