**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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of peripheral arterial disease</td>
<td>Treatment of peripheral arterial disease, including critical limb 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.</td>
</tr>
</tbody>
</table>

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>0263T</td>
<td>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</td>
</tr>
<tr>
<td>0264T</td>
<td>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</td>
</tr>
<tr>
<td>0265T</td>
<td>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</td>
</tr>
</tbody>
</table>

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Related Information

N/A

Evidence Review
Description

Critical limb ischemia due to peripheral arterial disease (PAD) results in pain at rest, ulcers, and creates a significant risk for limb loss. Injection or infusion of stem cells, either concentrated from bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source, is being evaluated for the treatment of critical limb ischemia.

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. 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 which stimulate the 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**

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.

The rationale of hematopoietic stem cell/bone marrow-cell therapy in PAD is to induce arteriogenesis by boosting the physiological repair processes. This requires large numbers of functionally active autologous precursor cells, and subsequently, a large quantity of bone marrow (eg, 240-500 mL) or other source of stem cells. The SmartPREP2® Bone Marrow Aspirate Concentrate System (Harvest Technologies) has been developed as a single-step point-of-care, bedside centrifugation system for the concentration of stem cells from bone marrow. The system is composed of a portable centrifuge and an accessory pack that contains processing kits including a functionally closed dual-chamber sterile processing disposable container. The SmartPREP2® system is designed to concentrate a buffy coat of 20 mL from whole-bone marrow aspirate of 120 mL.

The concentrate of bone marrow aspirate contains a mix of cell types, including lymphocytoid cells, erythroblasts, monocytoïd cells, and granulocytes. Following isolation and concentration, the hematopoietic stem cell/bone marrow concentrate is administered either intra-arterially or through multiple injections (20 to 60) into the muscle, typically in the gastrocnemius. Other methods of concentrating stem cells include the in vitro expansion of bone marrow-derived stem cells or use of granulocyte-macrophage colony-stimulating factor to mobilize peripheral blood mononuclear cells. There is some discrepancy in the literature regarding the nomenclature of cell types. Studies addressed in this policy include the use of mononuclear cells/monocytes and/or mesenchymal stem cells.

The primary outcome in stem cell therapy trials regulated by the U.S. Food and Drug Administration (FDA) is amputation-free survival. Other outcomes for CLI include the Rutherford criteria for limb status, healing of ulcers, the Ankle-Brachial Index (ABI), transcutaneous oxygen pressure (TcO2), and pain-free walking. The Rutherford criteria include ankle and toe pressure,
the level of claudication, ischemic rest pain, tissue loss, nonhealing ulcer, and gangrene. 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). An increase greater than 0.1 mmHg is considered to be clinically significant. TcPO2 is measured with an oxymonitor; the normal value is 70 to 90 mm Hg. Pain-free walking may be measured by time on a treadmill, or more frequently, by distance in a 400-meter walk.

Summary of Evidence

For individuals who have peripheral arterial disease 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 critical limb ischemia due to PAD consists primarily of phase 2 studies using various cell preparation methods and methods of administration. A meta-analysis of these 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. 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 the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1. A search of ClinicalTrials.gov in January 2018 and reviews by Powell (2012) and Bartel et al in (2013) identified a number of ongoing trials with concentrated, expanded, or stimulated stem cells for PAD (see Table 1).

The review by Powell evaluated the effects of biologic therapy in patients with CLI and described several products in phase 2 or 3 trials. The FDA recommended that the primary efficacy end point in a phase 3 CLI trial should be amputation-free survival. When the probability of this outcome is combined with the comorbid burden of CLI patients and variable natural history, a large numbers of patients (∼500) may be needed to evaluate clinical outcomes.
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01408901</td>
<td>PROgenitor Cell Release Plus Exercise to Improve functional Performance in PAD: The PROPEL Study (^\text{18})</td>
<td>210</td>
<td>Nov 2017 (ongoing)</td>
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<tr>
<td>NCT01679990(^a)</td>
<td>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)</td>
<td>172</td>
<td>April 2018</td>
</tr>
<tr>
<td>NCT02538978(^a)</td>
<td>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</td>
<td>224</td>
<td>Mar 2019</td>
</tr>
<tr>
<td>NCT01049919(^a)</td>
<td>MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia (CLI) in Subjects With Severe Peripheral Arterial Disease (PAD) (MOBILE)</td>
<td>152</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT03304821</td>
<td>Granulocyte-Macrophage Stimulating Factor (GM-CSF) in Peripheral Artery Disease: the GPAD-3 Study</td>
<td>176</td>
<td>Jun 2022</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
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<td></td>
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<tr>
<td>NCT01245335(^a)</td>
<td>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</td>
<td>97</td>
<td>Nov 2015 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
\(^a\) Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

*American Heart Association and American College of Cardiology*

The 2016 guidelines from the American Heart Association and 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 (CLI).\(^\text{14,15}\) Stem cell therapy for PAD was not addressed.
European Society of Cardiology

The 2016 guidelines from the American Heart Association and 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 (CLI). Stem cell therapy for PAD was not addressed.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

At least two devices that provide point-of-care concentration of bone marrow aspirate have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process:

- The SmartPReP2® Bone Marrow Aspirate Concentrate System, SmartPRep Platelet Concentration System (Harvest Technologies)
- The MarrowStim Concentration Kit and Marrow Stim™ Mini Concentration Kit (Biomet Biologics)

FDA product Code: JQC.

Ixmyelocel-T (Aastrom Biosciences now Vericel Corp.) is an expanded stem cell product where bone marrow aspirate is sent to a processing facility to be cultured in a bioreactor and expanded over a 2-week period. The expanded cell population is enriched with mesenchymal precursors and alternatively activated macrophages. This product is currently being evaluated in a pivotal Phase III trial regulated by the FDA.

Pluristem Therapeutics is developing allogeneic cell therapy derived from full-term placenta (PLX-PAD cells). This product has been tested in a Phase I trial in patients with critical limb ischemia.
References


## History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/09/11</td>
<td>New policy; add to Therapy section. Policy created with literature review through March 2011; considered investigational.</td>
</tr>
<tr>
<td>07/20/12</td>
<td>Replace policy. Policy updated with literature review through February 2012, rationale section revised. References 4 and 10 added. Policy statement is unchanged.</td>
</tr>
<tr>
<td>10/09/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>07/08/13</td>
<td>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.</td>
</tr>
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<td>08/20/13</td>
<td>Update Related Policies. Change title to 2.02.18.</td>
</tr>
<tr>
<td>07/31/14</td>
<td>Annual Review. Policy updated with literature review through April, 2014. References 5,14 added; others renumbered/removed. Policy statement unchanged.</td>
</tr>
<tr>
<td>07/14/15</td>
<td>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.</td>
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<tr>
<td>04/01/16</td>
<td>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.</td>
</tr>
<tr>
<td>09/01/17</td>
<td>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.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through</td>
</tr>
</tbody>
</table>
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- U.S. Department of Health and Human Services
  200 Independence Avenue SW, Room 509F, HHH Building
  Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
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