Medical Coverage Policy

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Cell-Based Therapy for Cardiac and Peripheral Arterial Disease

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Overview

This Coverage Policy addresses cell-based therapy using several cell types, proposed as a method to treat heart damage or peripheral arterial disease.

Coverage Policy

Transplantation of cells into the myocardium is considered experimental, investigational or unproven for ANY indication.

Autologous intra-arterial or intra-muscular bone marrow cell transplantation is considered not medically necessary for peripheral arterial disease and other occlusive conditions.

General Background

Cell-Based Therapy for Treatment of Damaged Myocardium

Cardiovascular-oriented research of cell-based therapy has largely been focused on myocardial repair, with particular emphasis on replacement and/or restoration of the damaged myocardium. Transplantable cell types being researched include skeletal myoblasts, bone marrow mononuclear cells (BM-MNC), hematopoietic stem cells (HSC), endothelial progenitor cells (EPC), mesenchymal stem cells (MSC), and pluripotent stem cell (PSC)-derived cardiomyocytes (CM) (PSC-CM). In clinical trials, route of delivery has included through vessels (intracoronary or intravenous) as well as direct injection into the heart muscle (intramyocardial or transendocardial).

Skeletal myoblasts are tissue-specific stem cells. Immature myoblasts contained in skeletal muscle can fuse with surrounding myoblasts or with damaged muscle fibers to regenerate functional skeletal muscle. Mesenchymal stem cells and hematopoietic stem cells have the capacity to differentiate into any type of cell, depending on their microenvironment. As they mature, they can acquire all the characteristics of the target tissue, such as myocardium and cardiac vessels. Cells may be delivered systemically or locally and must then proliferate to provide adequate new tissue prior to differentiating into functional cardiomyocytes that couple with the myocardium. Some cells may require significant manipulation prior to implantation. Stem cells may be delivered via infusion into the coronary arteries or injection into the ventricular wall. The mechanism of action of cell therapy for damaged myocardium is not entirely clear and is likely multifactorial.

U.S. Food and Drug Administration (FDA): Cell-Based Therapy for Treatment of Damaged Myocardium

The U.S. Food and Drug Administration (FDA) regulates cells that are processed in commercial laboratories, as well as the surgical devices used to inject the cells into the myocardium. There are several products being commercially developed for the treatment of damaged myocardium. However, the FDA has not yet issued approvals for any technology associated with the

transplantation of autologous cells for the treatment of damaged myocardium. Not FDA-Approved products include:

- MyoCell® (US Stem Cell, Inc, Sunrise, FL) is autologous muscle stem cell therapy for the treatment of severe heart damage in heart failure patients.
- MyoCell SDF-1™ (US Stem Cell, Inc, Sunrise, FL) is autologous cell therapy treatment for severe chronic damage in the heart; cells modified to express angiogenic proteins.
- AdipoCell™ (US Stem Cell, Inc, Sunrise, FL) The therapy involves the use of stem cells derived from the patient's own fat (adipose tissue) obtained using liposuction. Transplantation of AdipoCell™ is accomplished through endocardial implantations with an injection catheter.
- MultiStem® (invimestrocel) (Athersys Inc., Cleveland, OH) is developed from Multipotent Adult Progenitor Cells obtained from healthy adult bone marrow, for the treatment of diseases and conditions in the neurological, inflammatory and immune, cardiovascular disease areas, following hemorrhagic trauma/after severe traumatic injury.
- Ixmyelocel-T (Vericel Corporation, Cambridge, MA) is an expanded, multicellular therapy produced from a patient's own bone marrow (autologous) by selectively expanding two key types of bone marrow mononuclear cells. According to their website, Vericel states that in in 2017, the FDA designated the investigation of ixmyelocel-T for reduction in the risk of death and cardiovascular hospitalization in patients with chronic advanced heart failure due to ischemic dilated cardiomyopathy as a Fast Track Development Program.
- CardiAMP™ Cell Therapy (BioCardia® Inc., Sunnyvale, CA) is designed to be a comprehensive biotherapeutic heart failure solution, incorporating:
  - a proprietary molecular diagnostic to characterize the potency of a patient's own bone marrow cells and determine if they are an optimal candidate for therapy
  - a point of care processing platform to prepare cells at the patient's bedside
  - an optimized therapeutic formulation that builds on the total experience in the cardiac stem cell field to-date
  - a proprietary interventional delivery system that easily navigates a patient's vasculature to securely deliver the specific dosage of cells in a routine cardiac catheterization procedure (NCT02438306)
- CardiALLO Cell Therapy System (BioCardia® Inc., Sunnyvale, CA) uses culture-expanded, bone marrow-derived mesenchymal stem cells from a universal donor.

Professional Societies/Organizations: Cell-Based Therapy for Treatment of Damaged Myocardium
American College of Cardiology (ACC)/American Heart Association (AHA): The 2023 AHA/ACC Guideline for the Management of Patients With Chronic Coronary Disease noted the following under section 8.2. Evidence Gaps and Areas of Future Research Needs:

- In patients with CCD and refractory angina, research is needed to assess the utility of neuromodulation andthoracic spinal cord stimulation, therapeutic angiogenesis with cell/gene therapies, coronary sinus occlusion, and shockwave therapy.

The 2022 AHA/ACC Guideline for the Management of Heart Failure does not address cell-based therapy (Heidenreich, et al., 2022).

Literature Review: Cell-Based Therapy for Treatment of Damaged Myocardium
Cell therapy for damaged myocardium is a promising treatment option. Yan et al. (2024) notes that transplanted stem cells are poorly engrafted in the infarcted myocardium due to multiple factors. It has been shown that improving their retention often leads to improved functional outcomes. Strategies such as biomaterial utilization, cell combinations, and repeated IV injections can be optimized for cell-based therapy for MI. Future studies may focus on the selection of

patients with inflammation, the optimization of stem cells with better anti-inflammatory capacity, the combination of stem cells with biomaterials, and repeated intravenous delivery.

Studies and professional society opinion are needed to address a number of unresolved, technical and clinical issues, including optimum cell type, ideal number of cells, factors that promote engraftment, delivery methods and frequency, surgical delivery method and patient selection criteria.

Kavousi et al. (2024) conducted a meta-analysis of randomized controlled trials (RCTs) to investigate whether the transplantation of mesenchymal stem cells (MSCs) after heart failure (HF) could help improve clinical outcomes and myocardial performance indices. The intervention group receiving mesenchymal stem cell therapy by any route of administration (n=927) compared with the control groups receiving either no intervention or placebo in addition to the standard care (n=757). Routes included delivering cells via vessels (3 studies) or directly injected into the heart muscle (13 studies).

- Mortality: The pooled risk ratio showed that the risk of death in the MSC group was 21% lower compared to the control group ($p = 0.043$).
- Rehospitalization: The risk of re-hospitalization in the treatment group was lower in comparison with the control group, it was not statistically significant ($p = 0.06$). Meta-regression showed that trials injecting a higher number of cells to the patients had a higher risk of re-hospitalization and the risk of rehospitalization would increase by 1% with each million more cells injected. Subgroup analysis showed a significantly lower risk of rehospitalization in trials using
  - less than 100 million cells
  - autologous cells compared to trials using an allogeneic source of cells
- Major adverse cardiovascular events (MACE): No statistically significant difference in MACE between the MSC and control group.

The authors noted that that transplantation of MSCs for ischemic and dilated heart failure patients may reduce all-cause mortality; but these results should be interpreted with caution as the included studies used various routes of transplantation, number of cells, and duration of follow-up. Performance of large clinical trials with long duration of follow-up are needed.

Hosseinpour et al. (2024) conducted a meta-analysis of RCTs to determine and compare the cardiovascular outcomes and echocardiographic indices of mesenchymal stromal cell (MSCs) and bone-marrow mononuclear cell (BMMNCs) therapies in heart failure. The analysis included 36 RCTs (1549 HF patients receiving stem cells and 1252 patients in the control group). Transplantation of both types of cells in patients with HF resulted in a significant improvement in left ventricular ejection fraction (LEVF). Transplantation of the stem cells could not decrease the risk of major adverse cardiovascular events compared with controls. The authors note that future trials should primarily focus on the impact of stem cell transplantation on clinical outcomes of HF patients to verify or refute the findings of this study.

Abouzid et al. (2023) conducted a meta-analysis to assess the safety and efficacy of human umbilical cord-derived mesenchymal stromal cells (HUC-MSCs) therapy versus a placebo in patients with heart failure and MI. Three RCTs (201 patients) were included in this meta-analysis. There was an improvement in EF in patients who received HUC-MSCs compared to placebo after 12 months of transplantation ($p < 0.00001$). At the six-month follow-up period, there was no significant improvement in EF ($p = 0.43$), indicating that the duration of follow-up can shape the response to therapy. The authors concluded that findings indicate that HUC-MSC transplantation can improve EF but has no meaningful effect on readmission or mortality rates. They noted that existing evidence is insufficient to confirm the efficacy of HUC-MSCs for broader therapeutic applications. Therefore, additional double-blind RCTs with larger sample sizes are required.

Attar et al. (2022) conducted a meta-analysis that investigated the possible long-term clinical efficacy of bone marrow-derived mononuclear cells (BM-MNCs) on major adverse cardiovascular events (MACE) after acute myocardial infarction (AMI). The analysis included 23 randomized trials (n=2286 patients; n=1402 BM-MNC group, n=884 placebo group) that investigated the impact of BM-MNC therapy on clinical outcomes following acute MI. The primary outcomes measured CHF needing hospitalization, reinfarction and mortality with a follow ups ranging from 6–60 months. The secondary outcomes measured LV function with follow ups ranging from 3–12 months. There was a significantly lower risk of hospitalization for CHF and reinfarction in the intervention group compared to the control group (p=0.005, p=0.046 respectively). Cardiac-related mortality was not significantly different between the two study groups (p=0.207). Author noted limitations included heterogeneity across trials including differences in terms of treatment characteristics (cell dosage, cell isolation protocols, storage methods, and image modalities). Secondly, primary outcome of many studies included left ventricular ejection fraction (LVEF) and were not designed to monitor major cardiovascular events. No health disparities were identified by the investigators.

A Cochrane systematic review of 13 randomized controlled trials (RCTs) (n=762 [n=452 cell therapy and n=310 controls]) by Diaz-Navarro et al. (2021) assessed the effectiveness and safety of stem cell transplant in adults with non-ischemic dilated cardiomyopathy (DCM). The RCTs included compared the infusion of bone marrow-derived stem cells into the heart muscle with the usual-care (control) treatment in people diagnosed with DCM. Studies were classified and analyzed into three categories according to the comparison intervention, which consisted of no intervention/placebo, cell mobilization with cytokines, or a different mode of SCT. The studies included an average of 60 people aged 45 to 58.5 years and 50%–89% men in each trial. Following therapy, the participants were assessed from six months to five years, with most studies at one year. The outcomes measured all-cause mortality, safety, health-related quality of life (HRQoL), performance status and major adverse cardiovascular events. The evidence reviewed was considered low to very low quality due to the small number of events, the results were not similar across studies, risk of bias and issues with study design. The study reported that there is uncertainty regarding mortality, procedural complications, health-related quality of life and exercise capacity when comparing SCT to the control. Low-quality evidence suggested that SCT may slightly improve deterioration of heart function and may not increase the risk of abnormal heartbeats in people with DCM. There were not any studies that reported other relevant outcomes such as major cardiac adverse events. When comparing SCT plus cytokine to control there is uncertainty regarding mortality. SCT plus cytokine may not improve health-related quality of life but may improve exercise capacity as well as some physiological measures related to cardiac function (it is unclear the extent and clinical benefits for patients). No studies reported major cardiac adverse events or abnormal heartbeats. The authors concluded based on low quality evidence that more research is needed to establish the role of SCT in the treatment of DCM and the most effective therapies. No health disparities were identified by the investigators, however there were more males enrolled than females.

Yang et al. (2020) conducted a systematic review and meta-analysis of the evidence (n=43 RCTs) evaluating the short and long-term efficacy of mononuclear cell transplantation (MNC) in patients with myocardial infarction. The primary outcomes measured the changes in left ventricular ejection fraction (LVEF) and infarct size from baseline to follow-up. Secondary outcomes measured changes in the left ventricular end-systolic volume, left ventricular end-diastolic volume, brain natriuretic peptide/N-terminal pro–B-type natriuretic peptide, 6-minute walk test, New York Heart Association class, and major adverse cardiac events (MACE). Randomized controlled trials (RCTs) were eligible for inclusion if the transplanted cells were limited to unsorted MNC cell types without using pretreated or engineered MNCs; the patients had ST-segment elevation myocardial infarction (STEMI) and ischemic cardiomyopathy (ICM) with previous MI; and more than one month of follow-up was recorded. The follow-up ranged from 3–96 months. In the short-term follow-up, patients treated with MNCs demonstrated a significant increase in absolute LVEF of

2.21% ($p<0.001$) and 6.01% ($p<0.001$) in acute myocardial infarction (AMI) and ischemic cardiomyopathy studies, respectively. This effect was sustained in long-term follow-up. MNC therapy significantly reduced left ventricular end-systolic volume; however, infarct size, 6-minute walk test, New York Heart Association class, and MACE rates were comparable. Author noted limitations included the clinical heterogeneity across trials, particularly with regard to cell dosage, the timing of infusion, and imaging modalities. Another limitation was the small number of patients that were available for analysis of performance status and functional biomarkers. The authors concluded that MNC therapy may convey a modest but sustained increase in LVEF in ischemic cardiomyopathy patients. Well-designed, adequately powered RCTs using optimized delivery and doses are needed to support the outcome of this study.

Cell-Based Therapy for Peripheral Arterial Disease

An advanced form of Peripheral Arterial Disease (PAD) known as chronic limb-threatening ischemia (CTLI) is associated with gangrene formation, ulceration, and amputation of the limb. Nearly 10% PAD patients suffer from CLTI but > 50% eventually become candidate to amputation and/or succumb to death due to cardiovascular causes. Surgical and endovascular interventions to restore vascularization to the ischemic limb are effective but not suitable for all patients with PAD. Some patients who are then left with limited treatment options.

A promising approach to induce revascularization is therapeutic angiogenesis, which aims to induce the formation of new blood vessels from preexisting ones.
Numerous strategies to augment therapeutic angiogenesis have been tested in clinical studies, including cell, protein, and gene therapies, although the results have only shown minimal-to-moderate therapeutic benefit. Some of the limitations of the cell-based strategies include poor transplant cell survival, short-lived gene/protein delivery, harsh inflammatory host response, and suboptimal therapeutic dosing or frequency. Therapeutic cells that have been tested in clinical trials of PAD include bone marrow–derived mononuclear cells, mesenchymal stromal cells (MSCs), and subpopulations within these cell types based on surface antigen expression. Considering the variable approaches used by different groups, the wide range of cell types used, and the absence of standardized protocols for characterization of the cells and for evaluation of clinical outcome, there is substantial uncertainty regarding the effectiveness of various cell types in PAD patients (Huang, et al., 2024; Desai, et al., 2024; Frangogiannis, et al., 2019).

U.S. Food and Drug Administration (FDA): Cell-Based Therapy for Treatment of Peripheral Arterial Disease

- SmartPReP2 Centrifuge System (Harvest Technologies Corp, Inc. Plymouth, MA) received 510(k) approval on January 13, 2016 (K103340). The SmartPReP2 Centrifuge System is intended to be used in the clinical laboratory or intraoperatively at point-of-care for the safe and rapid preparation of platelet poor plasma and platelet concentrate from a small sample of blood and for preparation of a cell concentrate from bone marrow. Clinical trial NCT00595257 was a clinical trial using the SmartPReP2 BMAC System that assessed the use of autologous bone marrow aspirate concentrate (BMAC) for the treatment of non-reconstructable critical limb ischemia due to peripheral arterial occlusive disease.
- MarrowStim PAD Kit™ (Zimmer Biomet, Warsaw, Ind) is an investigational device (Wang, et al., 2017).
- Pluristem cell therapy product, PLX-PAD, is for the treatment of critical limb ischemia (CLI). PLX-PAD cell treatment (Pluri Biotech Ltd. [Israel] previously Pluristem Therapeutics, Inc.) (Pluristem) is not FDA-appoved. The company's website states that on January 9, 2018, the U.S. Food & Drug Administration (FDA) cleared the company's Expanded Access Program (EAP) for the use of its PLX-PAD cell treatment in patients with Critical Limb Ischemia (CLI). EAP allows the use of an investigational medical product outside of clinical trials and is usually granted in cases where patients are unsuitable for inclusion under the

study protocol and the patient's condition is life-threatening with an unmet medical need. (See NCT03006770, Norgren, et al., 2024).
- Ixmyelocel-T (Vericel Corporation, Cambridge, MA) is not FDA-approved. It is an expanded, multicellular therapy produced from a patient's own bone marrow (autologous) by selectively expanding two key types of bone marrow mononuclear cells (See Powell, et al., 2012).

Professional Societies/Organizations: Cell-Based Therapy for Treatment of Peripheral Arterial Disease

American College of Cardiology (ACC)/American Heart Association (AHA): The 2024 ACC/AHA Guideline for the Management of Lower Extremity Peripheral Artery Disease does not address bone marrow cell transplantation for PAD. Its states "Experimental therapies, such as angiogenic gene therapy and growth factors, are unavailable in clinical practice and are beyond the scope of this document" (Gornik, et al., 2024).

The use of cell therapy is not mentioned in the 2018 Appropriate Use Criteria for Peripheral Artery Intervention document (Bailey, et al., 2019).

Literature Review: Cell-Based Therapy for Treatment of Peripheral Arterial Disease
Despite extensive research, robust clinical evidence supporting the use of cell therapy in patients with critical limb ischemia is lacking. Randomized controlled clinical trial results are mixed. Considering the variable approaches used by different groups, the wide range of cell types used, and the absence of standardized protocols for characterization of the cells and for evaluation of clinical outcome, there is substantial uncertainty regarding the effectiveness of various cell types in PAD patients. There is a need for high-quality clinical studies to test the effectiveness of cell therapy in PAD patients. Moreover, studies are needed to identify the optimal selection criteria for treatment candidate, optimal cell types, method of administration, and to develop strategies that may enhance homing, survival and effectiveness of the injected cells.

Sojakova et al. (2024) conducted a systematic review of five randomized trials:
1. Walter et al. (2011) (PROVASA, N=40)
2. Teraa et al. (2015) (JUVENTAS, N=160)
3. Sharma et al. (2021) (N=81)
4. Powell et al (2011) (RESTORE-CLI, N=46)
5. Norgren et al. (2024) (PACE, N=213)

Sojakova et al. (2024) summarized the following: Stem cell therapy has a potential as a treatment for patients with CLTI, but the efficacy of autologous cell therapy (ACT) in clinical trials depends on the study design, inclusion and exclusion criteria, and endpoints. In the PACE or JUVENTAS study, patients were enrolled with high values of ankle and toe pressure or TcPO2. The Sharma trial included people with claudication without ulcers. These criteria do not meet the definition of CLTI. The primary endpoint of the PROVASA study was ABI, that is, the inexact parameter in patients with diabetes because of medial sclerosis.
Furthermore, the differences in the volume of injected suspension also impacted the effect of therapy. In accordance with the design of the JUVENTAS trial, these patients were treated with a smaller amount of stem cells. As we mentioned above, intramuscular routes of injection potentially contribute to better results for their local paracrine effects. Hence, this may have caused poorer results in studies with the intra-arterial administration of stem cells. Finally, regarding the control group, it depends on the choice of placebo, because using autologous serum could potentially influence the results of cell therapy; even small amounts of autologous cells can potentially improve the placebo effect.

In 2022 Moazzami et al. published an updated Cochrane review evaluating local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischemia that was initially published in 2011. Four randomized controlled trials (RCTs), with a combined total of 176 patients, met the inclusion criteria. Participants were randomized to receive either intramuscular cell implantation of bone marrow mononuclear cells (BMMNCs) or control. The control groups varied between studies, and included conventional therapy, diluted autologous peripheral blood, and saline. Three studies (n=123) reported there was no clear evidence that the administration of BMMNCs had an effect on mortality when compared to the control (very low-certainty evidence). All trials assessed changes in pain severity, but the trials used different forms of pain assessment tools, therefore the data was unable to be pooled. Three studies individually reported that there were not any differences in pain reduction between the groups and one study reported that pain reduction was greater in the BMMNC group compared to the control group (very low-certainty evidence). All four trials reported the rate of amputation at the end of the study period. However, the authors are uncertain if amputations were reduced in the BMMNC group compared to the control group because the potential benefit was lost when the concerning data was removed from the analysis. Ankle-brachial index was reported differently by each study, so data was not able to be pooled. Three studies reported no changes between groups, and one study reported greater improvement in ABI in the BMMNC group compared to the control group (very low-certainty evidence). One study reported pain-free walking distance, finding no clear difference between the groups (low-certainty evidence). Lastly, the data was pooled for the side effects reported during the follow-up, which did not show any clear difference between the groups (very low-certainty evidence). The review was unable to draw conclusions to support the use of local intramuscular transplantation of BMMNC for improving clinical outcomes in people with CLI due to the very low- to low-certainty evidence and limited data. Evidence from larger RCTs are needed in order to provide adequate statistical power to assess the role of this procedure. No health disparities were identified by the investigators.

Pu et al. (2022) conducted a meta-analysis of randomized controlled trials that assessed the safety and efficacy of autologous stem cell therapy in patients with atherosclerosis obliterans (ASO). Twelve RCTs (n=630 patients) met inclusion criteria. The criteria included: RCT trial design, a diagnosis of limb ischemia with ASO, the intervention group received autologous cell implantation, and the control group received placebo administration or standard care. The primary outcome measured the total amputation rate. There were ten RCTs (n=610 participants) that reported total amputation during the study follow-up period. The results showed that cell therapy significantly improved total amputation (p=0.004). Secondary outcomes measured major amputation, mortality, perfusion index and symptom (ABI, TcO2, rest pain score, and ulcer size). There were eight RCTs (n=485 participants) that showed cell therapy significantly reduced major amputation (p=0.02), significantly improved perfusion index (p=0.004) and significantly decreased rest pain score (p=0.007) when compared to placebo or standard care. In contrast, the results indicated that no significant difference was found between cell therapy and control groups regarding all-cause mortality (p=0.34) and reduction of ulcer size (p=0.39). Limitations noted by the authors included the small patient population, small amount of data and that most trials were designed for "no option" patients and results are not generalizable to all patients with PAD. Additionally, the studies in subgroup analyses were too small and the results should be interpreted with caution. Lastly, the heterogeneity of the included trials was inevitable due to the diversity of source and dosage of cell products, route of administration, follow-up duration, the severity of limb ischemia, and treatments in the control group. Additional RCT's with a larger sample size and a defined treatment design are needed. No health disparities were identified by the investigators.

Gao et al. (2019) conducted a systematic review and meta-analysis of randomized controlled trials that evaluated the efficacy and safety of autologous implantation of stem cells for peripheral artery disease. The primary outcomes measured amputation rate, major amputation rate, ulcer healing rate, and side effects. The second outcomes measured were ankle-brachial index (ABI),

transcutaneous oxygen tension (TcO2), rest pain score, and pain-free walking distance (PFWD). The review consisted of 27 RCTs (n=1186 patients) with 1280 limbs. Meta-analysis indicated that autologous stem cell therapy was more effective than conventional therapy on the healing rate of ulcers. There was also significant improvement in ABI, TcO2, and PFWD while significant reduction was shown in amputation rate and rest pain scores. But the result presented no significant improvement in major limb salvage. Eight trials reported the side effects of autologous stem cell therapy, and no serious side effects related to stem cells were reported. Author noted limitations included low quality studies with unclear or high risk of bias. Secondly, several studies had a small patient population with limited information for outcomes, such as adverse events. Thirdly, the included patients, types of stem cells, methods of transplantation, control group, and follow-up time were different among RCTs, which could cause heterogeneity. The author concluded that autologous stem cell therapy may have a positive effect on "no-option" patients with PAD, but presented no significant improvement in major limb salvage. The evidence is insufficient to due to high risk of bias and low-quality evidence of outcomes. Larger, randomized, double-blind, placebo-controlled, and multicenter trials are needed.

Abdul Wahid et al. (2018) conducted a Cochrane systematic review to compare the efficacy and safety of autologous cells derived from different sources, prepared using different protocols, administered at different doses, and delivered via different routes for the treatment of 'no-option' critical lower limb ischemia (CLI) patients. The trial included 7 randomized controlled trials (359 participants) that compared bone marrow-mononuclear cells (BM-MNCs) versus mobilized peripheral blood stem cells (mPBSCs), BM-MNCs versus bone marrow-mesenchymal stem cells (BM-MSCs), high cell dose versus low cell dose, and intramuscular (IM) versus intra-arterial (IA) routes of cell implantation. The authors concluded that based on low- and very low-quality evidence there are no clear differences between different stem cell sources and different treatment regimens of autologous cell implantation for outcomes such as all-cause mortality, amputation rate, ulcer healing, and rest pain for 'no option' CLI patients. Do to the lack of high-quality evidence the efficacy and long-term safety of autologous cells derived from different sources, prepared using different protocols, administered at different doses, and delivered via different routes for the treatment of 'no-option' CLI patients, cannot be determined. RCTs with larger numbers of participants and longer follow-up are needed to determine the efficacy and safety of cell-based therapy for CLI patients.

Xie et al. (2018) conducted a systematic review and meta-analysis of 23 randomized controlled trials (n=962 patients) to review evidence for the safety and efficacy of autologous stem cell therapy in critical limb ischemia (CLI). The included patients were ineligible for surgical or percutaneous revascularization. The studies included the following types of stem cells: bone marrow mononuclear cells, bone marrow mesenchymal stem cells, bone marrow stem cells, peripheral blood mononuclear cells, peripheral blood stem cells, CD34+, or CD133+ stem cells. The transplantation method of stem cell was intramuscular or intra-arterial. The mean follow-ups of the studies were three months, six months and 12 months. Meta-analysis showed that cell therapy significantly increased the probability of ulcer healing, angiogenesis and reduced the amputation rates ($p<0.00001$, $p<0.0001$, and $p<0.0001$, respectively) compared to the control group. Ankle-brachial index (ABI) and pain-free walking distance were significantly better in the cell therapy group than in the control group ($p<0.01$). The authors concluded that autologous stem cell therapy is safe and effective in CLI. However, higher quality and larger RCTs are required for further investigation to support clinical application of stem cell transplantation.

Rigato et al. (2017) performed a systematic review and meta-analysis to evaluate the safety and effectiveness of autologous cell therapy for intractable peripheral arterial disease (PAD)/critical limb ischemia (CLI). RCTs (19 studies/837 patients), non-randomized trials (n=7 studies/338 patients), and non-controlled studies (n=41 studies/1177 patients) were included in the analysis. Patients selected in studies were ineligible for surgical or percutaneous revascularization. The cell

products used in studies included BMMNCs, BMMSCs, or PBMNCs. The primary outcome was the rate of major amputation (defined as the removal of the limb of a part of it above the ankle) in the cell therapy versus control group. Secondary outcomes included amputation free survival and complete wound healing. Follow-up timeframes ranged from six to ten months. A primary meta-analysis was performed on all RCTs (n=19 studies). For the primary outcome, cell therapy was associated with a statistically significant reduction in amputation rate (p=0.0004) and increased probability of amputation-free survival (p=0.01). Mortality was not significantly improved (p=0.39). Cell therapy increased the probability of complete wound healing by 59%. In a sub-analysis of only randomized placebo-controlled trials (n=11 studies), cell therapy was associated with non-significant improvements in amputation rate (p=0.12), amputation-free survival (p=0.36), and wound healing (p=0.07). When the analysis was further limited to RCTs with a low risk of bias (n≤3 studies depending on the outcome), cell therapy appeared to confer no benefit for all endpoints. In general cell therapy was found to be associated with mild and primarily transient adverse events. The secondary analysis (i.e., all controlled trials; n=1175 patients) showed that approximately one amputation per year could potentially be avoided for every two patients successfully treated with cell therapy. Although the overall results of this analysis suggest that cell therapy may be safe and effective in treating this subset of patients with PAD/CLI, the validity is challenged by limitations of low-moderate quality and high heterogeneity of studies. Additional well designed RCTs with long-term follow-up are needed to confirm these findings.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Cellular Therapy (30.8)	'Long standing'
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven when used to report transplantation of cells into the myocardium:

CPT®* Codes	Description
33999	Unlisted procedure, cardiac surgery
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous
93799	Unlisted cardiovascular service or procedure

HCPCS Codes	Description
C9782	Blinded procedure for New York Heart Association (NYHA) Class II or III heart failure, or Canadian Cardiovascular Society (CCS) Class III or IV chronic refractory angina; transcatheter intramyocardial transplantation of autologous bone marrow cells (e.g., mononuclear) or placebo control, autologous bone marrow harvesting and preparation for transplantation, left heart catheterization including ventriculography, all laboratory services, and all imaging with or without guidance (e.g., transthoracic echocardiography, ultrasound, fluoroscopy), performed in an approved investigational device exemption (IDE) study
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition

Considered Not Medically Necessary when used to report autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral arterial disease and other occlusive conditions:

CPT®* Codes	Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• No clinical policy statement changes.	5/15/2025
Annual Review	• No clinical policy statement changes.	5/15/2024