MEDICAL POLICY – 2.02.18
Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

BCBSA Ref. Policy: 2.02.18
Effective Date: Aug. 1 2022
Last Revised: July 11, 2022
Replaces: N/A

RELATED MEDICAL POLICIES:
- 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)
- 8.01.55 Stem Cell Therapy for Peripheral Arterial Disease

Select a hyperlink below to be directed to that section.

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

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

A progenitor cell is an immature cell that can turn into different types of mature cells. Using progenitor cells is being studied as a possible way to repair or grow new tissue, including heart tissue. While there are many procedures and drugs that treat heart disease, none of them actually repair or regrow heart tissue. Progenitor cell therapy is being explored as a way to do this. While early studies show that it might bring some benefit, there’s not yet enough scientific evidence to confirm that it works. More and larger studies are needed. For this reason, progenitor cell therapy for heart disease is considered investigational (unproven).

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.
Progenitor cell therapy describes the use of multipotent cells of various cell lineages (autologous or allogeneic) for tissue repair and/or regeneration. Progenitor cell therapy is being investigated for the treatment of damaged myocardium resulting from acute or chronic cardiac ischemia and for refractory angina.
Background

Ischemia

Ischemia is the most common cause of cardiovascular disease and myocardial damage in the developed world. Despite impressive advances in treatment, ischemic heart disease is still associated with high morbidity and mortality. According to the American Heart Association, coronary heart disease has a prevalence of 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people. For all age strata, the incidence of myocardial infarction is higher in Black males than in Black females, White males, and White females. Heart failure has the highest prevalence among Black males (3.6%) followed by Black females (3.3%), Hispanic and White males (both 2.4%), Asian males (1.9%), Hispanic females (1.7%), White females (1.4%), and Asian females (0.7%). Age-adjusted death rates per 100,000 individuals with coronary heart disease and heart failure are higher for Black males and females than their counterparts of other races.

Treatment

Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments do not reverse existing heart muscle damage. Treatment with progenitor cells (i.e., stem cells) offers potential benefits beyond those of standard medical care, including the potential for repair and/or regeneration of damaged myocardium. Potential sources of embryonic and adult donor cells include skeletal myoblasts, bone marrow cells, circulating blood-derived progenitor cells, endometrial mesenchymal stem cells (MSCs), adult testis pluripotent stem cells, mesothelial cells, adipose-derived stromal cells, embryonic cells, induced pluripotent stem cells, and bone marrow mesenchymal stem cells, all of which can differentiate into cardiomyocytes and vascular endothelial cells for regenerative medicine advanced therapy (RMAT). The RMAT designation may be given if: (1) the drug is a regenerative medicine therapy (i.e., a cell therapy), therapeutic tissue engineering product, human cell and tissue product, or any combination product; (2) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and (3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs.
Summary of Evidence

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes two phase three randomized controlled trials (RCTs), numerous small, early phase RCTs, and meta-analyses of these RCTs. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. Limited evidence on clinical outcomes has suggested that there may be benefits from improving left ventricular ejection fraction (LVEF), reducing recurrent myocardial infarction (MI), decreasing the need for further revascularization, and perhaps decreasing mortality. Although a recent, large, individual patient data meta-analysis reported no improvement in these outcomes. No adequately powered trial has reported benefits in clinical outcomes (e.g., mortality, adverse cardiac outcomes, exercise capacity, quality of life). Overall, this evidence has suggested that progenitor cell treatment may be a promising intervention, but robust data on clinical outcomes are lacking. High-quality RCTs, powered to detect differences in clinical outcomes, are needed to answer this question. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes two phase three RCTs with more than 100 participants, two phase 2 RCTs with more than 100 participants, systematic reviews of smaller, early-phase RCTs, and a nonrandomized comparative trial. The relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. The studies included in the meta-analyses reported only a small number of clinical outcome events. Two phase 2 RCTs (CONCERT-HF and ixCELL-DCM) found significant benefit on heart failure-related death and other cardiac events with cell therapy compared to placebo. A well-conducted, phase 3 RCT trial failed to demonstrate superiority of cell therapy for its primary composite outcome that included death, worsening heart failure events, and other multiple events. The nonrandomized Stem Cell Transplantation in 191 Patients With Chronic Heart Failure (STAR-Heart) trial showed a mortality benefit as well as favorable hemodynamic effect, but a lack of randomization limits interpretation due to the concern about selection bias and differences in known and unknown prognostic variables at baseline between both arms. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have refractory angina who receive progenitor cell therapy, the evidence includes a systematic review of RCTs, phase 2 trials, and a phase 3 pivotal trial. The relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. The only phase 3 trial identified was terminated early and insufficiently powered
to evaluate clinical outcomes. Additional larger trials are needed to determine whether progenitor cell therapy improves health outcomes in patients with refractory angina. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### Ongoing and Unpublished Clinical Trials

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

#### 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>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT04614467</td>
<td>A Double-Blind, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of CLBS16 in Subjects With Coronary Microvascular Dysfunction and Without Obstructive Coronary Artery Disease</td>
<td>105</td>
<td>Oct 2022</td>
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<tr>
<td>NCT02323620</td>
<td>The Impact of Repeated Intracoronary Injection of Autologous Bone-marrow Derived Mononuclear Cells for Left Ventricle Contractility and Remodeling in Patients With STEMI Prospective Randomized Study (RACE-STEMI)</td>
<td>200</td>
<td>Dec 2022</td>
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<tr>
<td>NCT01693042</td>
<td>Randomized Controlled Trial to Compare the Effects of Single Versus Repeated Intracoronary Application of Autologous Bone Marrow-derived Mononuclear Cells on Total and SHFM-predicted Mortality in Patients With Chronic Post-infarction Heart Failure (REPEAT)</td>
<td>81</td>
<td>Jan 2025</td>
</tr>
<tr>
<td>NCT03455725</td>
<td>Prospective, multi-center, 2:1 randomized (Treatment vs Sham Control), blinded trial comparing 2 parallel groups of patients with CMI treated with CardiAMP cell therapy system vs sham treatment (CardiAMP CMI)</td>
<td>343</td>
<td>Dec 2026</td>
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<tr>
<td><strong>Unpublished</strong></td>
<td></td>
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<td></td>
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<tr>
<td>NCT No.</td>
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<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>NCT03129568</td>
<td>A Prospective Phase 1 Trial of Cardiac Progenitor Cell Therapy in Children With Dilated Cardiomyopathy</td>
<td>5</td>
<td>Dec 2020</td>
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<tr>
<td>NCT01781390*</td>
<td>A Prospective, Double Blind, Randomized, Placebo-controlled Clinical Trial of Intracoronary Infusion of Immunoselected, Bone Marrow-derived Stro3 Mesenchymal Precursor Cells (MPC) in the Treatment of Patients With ST-elevation Myocardial Infarction (AMICI)</td>
<td>106</td>
<td>Apr 2021</td>
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<tr>
<td>NCT03418233*</td>
<td>Regeneration of Ischemic Damages in Cardiovascular System Using Wharton's Jelly as an Unlimited Source of Mesenchymal Stem Cells for Regenerative Medicine. Project of the National Centre for Research and Development (Poland) 'STRATEGMED II'. Randomized Clinical Trial to Evaluate the Regenerative Capacity of CardioCell in Patients With Chronic Ischaemic Heart Failure (CIHF)</td>
<td>115</td>
<td>Mar 2021</td>
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<tr>
<td>NCT02501811</td>
<td>A Phase II, Randomized, Placebo-Controlled Study of the Safety, Feasibility, &amp; Efficacy of Autologous Mesenchymal Stem Cells &amp; C-kit+ Cardiac Stem Cells, Alone or in Combination, Administered Transendocardially in Subjects With Ischemic HF</td>
<td>125</td>
<td>July 2020</td>
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<tr>
<td>NCT02032004*</td>
<td>Efficacy and Safety of Allogeneic Mesenchymal Precursor Cells (Rexlemestrocel-L) for the Treatment of Heart Failure (DREAM HF-1)</td>
<td>566</td>
<td>May 2020</td>
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NCT: national clinical trial
* Denotes industry-sponsored or cosponsored trial

**Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. 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 College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions

In 2015, the American College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions issued a Focused Update on Primary Percutaneous Coronary Interventions for Patients With ST-Elevation Myocardial Infarction. This guideline was an update of the 2011 guideline for percutaneous coronary intervention and the 2013 guideline on managing ST-elevation myocardial infarction. In 2021, these same organizations published a guideline on coronary artery revascularization. Progenitor cell therapy was not mentioned in this update or in the 2013 guidelines.

The most recent guidance on treatment of heart failure with reduced ejection fraction from the American College of Cardiology foundation (2021) does not mention progenitor cell therapy.

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

Multiple progenitor cell therapies such as MyoCell® (U.S. Stem Cell, formerly Bioheart), ixmyelocel-T (Vericel, formerly Aastrom Biosciences), MultiStem® (Athersys), and CardiAMP™ (BioCardia) are being commercially developed, but none has been approved by the U.S. Food and Drug Administration (FDA) so far.

MyoCell comprises patient autologous skeletal myoblasts that are expanded ex vivo and supplied as a cell suspension in a buffered salt solution for injection into the area of damaged myocardium. In 2017, U.S. Stem Cell reprioritized its efforts away from seeking RMAT designation for MyoCell. The expanded cell product enriched for mesenchymal and macrophage lineages might enhance potency. Vericel has received RMAT designation for Ixmyelocel-T.

MultiStem® is an allogeneic bone marrow-derived adherent adult stem cell product that has received RMAT designation.

The CardiAMP Cell Therapy system consists of a proprietary assay to identify patients with a high probability to respond to autologous cell therapy, a proprietary cell processing system to
isolate process and concentrate the stem cells from a bone marrow harvest at the point of care, and a proprietary delivery system to percutaneously inject the autologous cells into the myocardium. BioCardia has received an investigational device exemption from the FDA to perform a trial of CardiAMP and is designated as an FDA Breakthrough Device.

References


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**History**

<table>
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<tr>
<th>Date</th>
<th>Comments</th>
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<td>07/13/04</td>
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<td>05/26/06</td>
<td>Update Scope and Disclaimer - No other changes.</td>
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<td>Replace Policy - Policy updated with literature search; no change to the policy statement. Description, Rationale, and References sections completely revised based on 2008 TEC Assessment. Title also updated to include “Progenitor” after Autologous and “due to Ischemia” after Damaged Myocardium.</td>
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<td>09/17/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<td>Replace policy. Policy updated with literature search through May 15, 2013; references 15, 22, 29 and 30 added and references reordered; policy statements unchanged.</td>
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<td>Annual Review. Policy updated with literature review through May 18, 2015; references 15, 29-30, and 33-34 added; references 35-36 deleted. Policy statements unchanged.</td>
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<td>Annual Review, approved August 9, 2016. Policy updated with literature review through July 14, 2016; no change to the policy statement. Removed code 38206</td>
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<td>03/01/17</td>
<td>Annual Review, approved February 14, 2017. Policy updated with literature review through October 10, 2016; references 4-5, 8, and 21 added; Rationale revised and some references removed. Policy statements unchanged.</td>
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<td>06/09/17</td>
<td>Coding update; updated description for CPT code 38241.</td>
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