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, 2018
Last Revised: July 13, 2018
Replaces: N/A

RELATED MEDICAL POLICIES:
8.01.55 Stem Cell Therapy for Peripheral Arterial Disease

Select a hyperlink below to be directed to that section.

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EVIDENCE REVIEW | REFERENCES | HISTORY

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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.

Policy Coverage Criteria
Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic stem cells, is considered investigational as a treatment of damaged myocardium.

Infusion of growth factors (ie, granulocyte colony stimulating factor [GCSF]) is considered investigational as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
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<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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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.

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 (ie, 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 MSCs, all of which are able to differentiate into cardiomyocytes and vascular endothelial cells.

The mechanism of benefit after treatment with progenitor cells is not entirely understood. Differentiation of progenitor cells into mature myocytes and engraftment of progenitor cells into areas of damaged myocardium has been suggested in animal studies using tagged progenitor cells. However, there is controversy concerning whether injected progenitor cells engraft and differentiate into mature myocytes in humans to a degree that might result in clinical benefit. It also has been proposed that progenitor cells may improve perfusion to areas of ischemic myocardium. Basic science research also suggested that injected stem cells secrete cytokines with anti-apoptotic and pro-angiogenesis properties. Clinical benefit may result if these paracrine factors limit cell death from ischemia or stimulate recovery. For example, myocardial protection can occur through modulation of inflammatory and fibrogenic processes. Alternatively, paracrine factors may affect intrinsic repair mechanisms of the heart through neovascularization, cardiac metabolism and contractility, increase in cardiomyocyte proliferation, or activation of resident stem and progenitor cells. The relative importance of these proposed paracrine actions depends on the age of the infarct (eg, cytoprotective effects in acute ischemia
and cell proliferation in chronic ischemia). Investigation of the specific factors induced by administration of progenitor cells is ongoing.

There are also various potential delivery mechanisms for donor cells, encompassing a wide range of invasiveness. Donor cells can be delivered via thoracotomy and direct injection into areas of damaged myocardium. Injection of progenitor cells into the coronary circulation also is done using percutaneous, catheter-based techniques. Finally, progenitor cells may be delivered intravenously via a peripheral vein. With this approach, the cells must be able to target damaged myocardium and concentrate at the site of myocardial damage.

Adverse effects of progenitor cell treatment include risks of the delivery procedure (eg, thoracotomy, percutaneous catheter-based) and risks of the donor cells themselves. Donor progenitor cells can differentiate into fibroblasts rather than myocytes. This may create a substrate for malignant ventricular arrhythmias. There also is a theoretical risk that tumors (eg, teratomas) can arise from progenitor cells, but the actual risk in humans is currently unknown.

Summary of Evidence

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 phase 3 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, reducing recurrent myocardial infarction, decreasing 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 (eg, 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 the effects of the technology on health outcomes.

For individuals who have chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 phase 3 RCTs with more than 100 participants, systematic reviews of smaller, early-phase RCTs, and a nonrandomized comparative trial. 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.
These findings from early phase 2 trials need to be corroborated in larger phase 3 trials. 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 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 the effects of the technology on health outcomes.

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. 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 the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently 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>
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<tbody>
<tr>
<td>Ongoing</td>
<td></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>105</td>
<td>Jun 2018</td>
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<tr>
<td>NCT01969890</td>
<td>Phase III Study on STem cElIs Mobilization in Acute Myocardial Infarction (STEM-AMI)</td>
<td>1530</td>
<td>Oct 2018 (suspended)</td>
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<tr>
<td>NCT02323620</td>
<td>The Impact of Repeated Intracoronary Injection of Autologous Bone-marrow Derived Mononuclear Cells for</td>
<td>200</td>
<td>Dec 2018</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td></td>
<td>Left Ventricle Contractility and Remodeling in Patients With STEMI Prospective Randomized Study (RACE-STEMI)</td>
<td></td>
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<tr>
<td>NCT00526253</td>
<td>A Multicenter Study to Assess the Safety and Cardiovascular Effects of Myocell™ Implantation by a Catheter Delivery System in Congestive Heart Failure Patients Post Myocardial Infarction(s)</td>
<td>170</td>
<td>Feb 2019</td>
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<tr>
<td>NCT02032004</td>
<td>A Double-blind, Randomized, Sham-procedure-controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (CEP-41750) in Patients With Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology (STEM-AMI)</td>
<td>600</td>
<td>Feb 2019</td>
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<tr>
<td>NCT01569178</td>
<td>The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All Cause Mortality in Acute Myocardial Infarction (BAMI)</td>
<td>350</td>
<td>Oct 2019</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 (CIRCULATE)</td>
<td>115</td>
<td>Dec 2020</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>676</td>
<td>Jan 2025</td>
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<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>
</tr>
</tbody>
</table>

NCT: national clinical trial

a Denotes industry-sponsored or cosponsored trial
Practice Guidelines and Position Statements

In 2013, American College of Cardiology Foundation and the American Heart Association issued joint guidelines for the management of ST-segment elevation myocardial infarction. Progenitor cell therapy was not recommended.

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.

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Progenitor cells are included in these regulations. FDA marketing clearance is not required when autologous cells are processed on site with existing laboratory procedures and injected with existing catheter devices. Several cell products are expanded ex-vivo and require FDA approval. The 21st Century Cures Act (December 2016) established new expedited product development programs including one for regenerative medicine advanced therapy (RMAT). The RMAT designation may be given if: (1) the drug is a regenerative medicine therapy (ie, 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.

Multiple progenitor cell therapies such as MyoCell® (U.S. Stem Cell, formerly Bioheart), Ixmyelocel-T (Vericel, formerly Aastrom Biosciences), MultiStem® (Athersys), and CardiAMPTM (BioCardia) are being commercially developed, but none have been approved by the 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®.
Ixmyelocel-T is an expanded multicellular therapeutic product produced from a patient’s bone marrow by selectively expanding bone marrow mononuclear cells for 2 weeks. 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.

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 FDA to perform a trial of CardiAMP™.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<td>07/13/04</td>
<td>Add to Medicine section, Cardiology subsection - New Policy</td>
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<td>06/14/05</td>
<td>Replace Policy - Policy updated with literature review; no change to policy statement.</td>
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<td>04/11/06</td>
<td>Replace Policy - Policy updated with literature review; no change to policy statement.</td>
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<td>05/26/06</td>
<td>Update Scope and Disclaimer - No other changes.</td>
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<td>04/10/07</td>
<td>Replace Policy - Policy updated with literature search; references added. No change in policy statement.</td>
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<td>08/12/08</td>
<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>12/08/09</td>
<td>Replace Policy - Policy updated with literature search; no change to the policy statement. References added.</td>
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<td>09/14/10</td>
<td>Replace Policy - Policy updated with literature review through May 2010; no change to the policy statement. References have been added, deleted and reordered.</td>
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<td>08/09/11</td>
<td>Replace Policy – Policy updated with literature search through April 2011; references added and reordered; policy statements unchanged.</td>
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<td>08/20/12</td>
<td>Replace policy. Policy updated with literature search through March 2012; references 12, 14, 22 added and references reordered; 1 reference removed; policy statements unchanged. Title changed to Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia.</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>08/16/13</td>
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<tr>
<td>09/03/14</td>
<td>Annual Review. Policy updated with literature review through May 7, 2014; references 13-14, 22, 27, 32-34, 39-40 added; others renumbered or removed. Policy statements</td>
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<td>Date</td>
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<td>08/11/15</td>
<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>09/01/16</td>
<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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<tr>
<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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<tr>
<td>06/09/17</td>
<td>Coding update; updated description for CPT code 38241.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
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