Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

Policy Number: 2.02.18  Last Review: 8/2017  Origination: 4/2013  Next Review: 8/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for progenitor cell therapy for the treatment of damaged myocardium due to ischemia. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
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 (i.e., 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.

Considerations
There are no specific codes for this procedure, either describing the laboratory component of processing the harvested autologous cells or for the implantation procedure. In some situations, the implantation may be an added component of a scheduled coronary artery bypass graft (CABG); in other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure.

Description of Procedure or Service

<table>
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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<td>Individuals:</td>
<td>Interventions of interest</td>
<td>Comparators of interest</td>
<td>Relevant outcomes include:</td>
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<td>With acute</td>
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<td>are:</td>
<td>• Disease-specific survival</td>
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<td>cardiac ischemia</td>
<td>Progenitor cell therapy</td>
<td>Standard therapy</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.

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 randomized controlled trials (RCTs) with 200 patients, numerous small 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 even 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 a nonrandomized comparative trial and systematic reviews of smaller RCTs. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. Studies included in meta-analyses have reported only a handful of clinical outcome events, too few for meaningful analysis. Results of the nonrandomized trial are encouraging, because this is the first controlled trial that has reported a significant mortality benefit for progenitor cell treatment. However, other clinical outcomes were not reported with sufficient methodologic rigor to permit conclusions. 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 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.

Background
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. Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments are not able to reverse existing damage to heart muscle. (1, 2) 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. The 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 following 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 actually engraft and differentiate into mature myocytes in humans to a degree that might result in clinical benefit. It has also been proposed that progenitor cells may improve perfusion to areas of ischemic myocardium. Basic science research also suggests that injected stem cells secrete cytokines with anti-apoptotic and pro-angiogenesis properties. Clinical benefit may result if these paracrine factors are successful at limiting cell death from ischemia or stimulating recovery. For example, myocardial protection can occur through modulation of inflammatory and fibrogenic process. Alternatively, paracrine factors might 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 will depend on the age of the infarct, e.g., cytoprotective effects with acute ischemia versus cell proliferation with chronic ischemia. Investigation of the specific factors that are induced by administration of progenitor cells is ongoing.

There are also a variety of 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 can also be done using percutaneous, catheter-based techniques. Finally, progenitor cells can 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 treatment with progenitor cells include the risk of the delivery procedure (e.g., thoracotomy, percutaneous catheter-based, etc.) and the 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 is also a theoretical risk that tumors, such as teratomas, can arise from progenitor cells, but the actual risk of this occurring in humans is not known at present.

**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. Hematopoietic 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.

MyoCell® (Bioheart, Sunrise, FL) 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. MyoCell® SDF-1 (Bioheart) is similar to MyoCell®, but before injection, myoblast cells are genetically modified to release excess stromal-derived factor-1 (SDF-1). Increased SDF-1 levels at the site of myocardial damage may accelerate recruitment of native stem cells to increase tissue repair and neovascularization. For both products, myoblast isolation and expansion occur at a single reference laboratory (Bioheart); both products are therefore subject to FDA approval. Currently, neither has been cleared by FDA. Implantation may require use of a unique catheter delivery system (eg, MyoCath [Bioheart]) that has been cleared by FDA.

An allogeneic human mesenchymal stem cell (hMSC) product (Prochymal®; Osiris Therapeutics) under investigation for the treatment of acute myocardial infarction (AMI). Prochymal® (also referred to as Provaceel®; Osiris) is a highly purified preparation of ex vivo cultured adult hMSCs isolated from the bone marrow of healthy young adult donors. Prochymal® has been granted fast track status by FDA for Crohn disease and graft-versus-host disease (GVHD), and has orphan drug status for GVHD from FDA and the European Medicines Agency.

Ixmyelocel-T (Vericel, formerly Aastrom Biosciences) is an autologous bone marrow-derived multicellular therapy produced by expanding bone marrow mononuclear cells. Ixmyelocel-T was cleared for marketing by FDA through the orphan drug process for the treatment of ischemic dilated cardiomyopathy, based on results of a phase 2b study.
MultiStem® (Athersys) is an allogeneic bone marrow–derived adherent adult stem cell product. MultiStem® was cleared for marketing by FDA through the orphan drug process for GVHD and has received authorization from FDA for a phase 2 trial for treatment of AMI with an adventitial delivery system. In September 2016, under a Special Protocol Assessment of FDA, Athersys received approval of the design and analysis for its phase 3 trial (MultiStem Administration for Stroke Treatment and Enhanced Recovery Study-2 [MASTERS-2]) on the use of MultiStem® for treating patients who had experienced an ischemic stroke.

**Rationale**

This evidence review was originally created in April 2004 and derived in part from a 2008 TEC Assessment,(3) with the literature subsequently updated on a periodic basis using the MEDLINE database. The most recent literature update was performed through October 10, 2016.

Progenitor cell therapy for the treatment of damaged and ischemic myocardium is a rapidly evolving field. There are several areas of uncertainty, including patient selection, cell type, and procedural details (eg, timing and mode of delivery).(4) The overall body of evidence is characterized by numerous randomized controlled trials (RCTs) and a number of meta-analyses of these RCTs. A 2015 meta-analysis by Afzal et al (search through August 2014) identified 48 RCTs on bone marrow cell (BMC) therapy for acute or chronic ischemic heart disease.(5) Selected RCTs were mostly small in size and highly variable in terms of patient populations, types of progenitor cells used, and delivery methods. Some cell products have achieved orphan drug status from the U.S. Food and Drug Administration based on phase 2 trials. The present evidence review focuses on phase 3 trials with at least 100 patients per arm and systematic reviews of RCTs.

In the present evidence review, relevant clinical trials and meta-analyses are reviewed for 3 different indications: (1) acute cardiac ischemia (myocardial infarction [MI]); (2) chronic cardiac ischemia; and (3) refractory or intractable angina in patients who are not candidates for revascularization. This evidence review focuses on the impact of progenitor cell therapy on clinical outcomes but also includes data on physiologic outcomes, such as change in left ventricular ejection fraction (LVEF).

**TREATMENT WITH PROGENITOR CELLS FOR ACUTE CARDIAC ISCHEMIA**

**Systematic Reviews**

**Bone Marrow Cells**

Four meta-analyses published from 2014 to 2015, including a Cochrane review and an individual patient data (IPD) meta-analysis evaluating the use of progenitor cell therapy for the treatment of acute ischemia (MI), are described below. Table 1 details the reviews and summarizes the analyses.
Two meta-analyses on BMC infusion for the treatment of acute myocardial infarction (AMI) were published in 2014 and included many of the same studies. Delewi et al published a meta-analysis of 16 trials (total N=1641 patients). (6) The meta-analyses of de Jong et al included 22 RCTs (total N=1513 patients). (7) Thirteen RCTs (1300 patients) appeared in both systematic reviews. Both analyses found statistically significant increases in LVEF with BMC infusion compared with placebo. Subgroup analyses by Delewi et al showed that the treatment benefit was greater among younger patients (age <55 years) and among patients with more severely depressed LVEF at baseline (<40%), while subgroup analysis by de Jong et al that included only trials with end points derived from magnetic resonance imaging (MRI; 9 trials), showed that the therapy did not have an effect on cardiac function, volumes, or infarct size. With median follow-up of 6 months, there was no difference between BMC infusion and placebo in all-cause mortality, cardiac mortality, restenosis rate, thrombosis, target vessel revascularization, stroke, recurrent AMI, or implantable cardioverter defibrillator implantations. Based on these findings, de Jong et al concluded that, although safe, intracoronary infusion of BMCs did not improve clinical outcomes.

A 2015 Cochrane review on stem cell treatment for AMI included 41 trials (total N=2732 patients). (8) Many were small trials and conducted outside the United States; others were reported only as conference proceedings. Studies varied by cell dose, cell type, and timing of administration. Overall, cell treatment was not associated with any changes in the risk of all-cause mortality, cardiovascular mortality, or a composite measure of mortality, reinfarction, and rehospitalization for heart failure at long-term follow-up. Reviewers concluded that there was insufficient evidence for a beneficial effect of cell therapy for patients experiencing an AMI and that adequately powered trials are needed.

Gyöngyösi et al (2015) conducted a IPD meta-analysis of 12 RCTs (total N=1252 patients), including the REPAIR-AMI trial (reviewed below), using a collaborative, multinational database, ACCRUE (meta-Analysis of Cell-based CaRdiac study; NCT01098591). (9) Eight trials had low risk of bias, and 4 single-blind (assessor) trials had medium-to-low risk of bias. Adjusted (for cardiovascular risk factors) random-effects meta-analyses showed no effect of cell therapy on the primary end points of major adverse cardiac and cerebrovascular events (a composite of all-cause death, AMI recurrence, coronary target vessel revascularization, and stroke). The meta-analysis was limited by variations in the time from AMI to cell delivery (median, 6.5 days) and in imaging modalities used to assess cardiac function (MRI, single-proton emission computed tomography, angiography, echocardiography).

**Granulocyte Colony Stimulating Factor**

The body of evidence on the use of granulocyte colony stimulating factor (G-CSF) as a treatment for coronary heart disease is smaller than that for the use of stem cells. A few RCTs on treatment of acute ischemia have reported physiologic outcomes. Additionally, meta-analyses of the available trials have been published. Moazzami et al (2013) published a Cochrane review of G-CSF for AMI. (10) Literature was searched in November 2010, and 7 small, placebo-controlled
randomized trials (total N=354 patients) were included. Overall risk of bias was considered low. All-cause mortality did not differ between groups (relative risk [RR], 0.6; 95% confidence interval [CI], 0.2 to 2.8; p=0.55; I²=0%). Similarly, change in LVEF, left ventricular (LV) end systolic volume, and LV end diastolic volume did not differ between groups. Evidence was insufficient to draw conclusions about the safety of the procedure. Reviewers concluded there was lack of evidence for benefit of G-CSF therapy in patients with AMI.

**Table 1. Summary of Systematic Reviews and Meta-Analyses of the Use of Progenitor Cell Therapy for the Treatment of Acute Ischemia Outcome**

<table>
<thead>
<tr>
<th>Outcome Study (Year)</th>
<th>Dates</th>
<th>Trials</th>
<th>Patients</th>
<th>Study Design</th>
<th>Mean Time Between Acute Event and Cell Infusion</th>
<th>Trial Duration, mo</th>
<th>ΔLVEF, Mean Change or % Change</th>
<th>Risk All-Cause Mortality</th>
<th>Risk of CV Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delewi et al (2014) 6</td>
<td>1980-Feb 2013</td>
<td>16</td>
<td>1641</td>
<td>RCT</td>
<td>≤1 mo</td>
<td>• Median, 6&lt;br&gt; • Range, 3-6</td>
<td>2.55% (1.83% to 3.26%)&lt;br&gt;I²=84%</td>
<td>NR&lt;br&gt;NR</td>
<td></td>
</tr>
<tr>
<td>De Jong et al (2014) 7</td>
<td>Jan 2002-Sep 2013</td>
<td>22</td>
<td>1513</td>
<td>RCT</td>
<td>≤1 mo</td>
<td>• Median, 6&lt;br&gt; • Range, 3-60</td>
<td>2.10% (0.68% to 3.52%)&lt;br&gt;I²=80%</td>
<td>0.68a (0.36 to 1.31)&lt;br&gt;0.73a (0.32 to 1.65)</td>
<td></td>
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<tr>
<td>Fisher et al (2015) 8</td>
<td>Through Mar 2015</td>
<td>41</td>
<td>2732</td>
<td>RCT</td>
<td>≤14 d</td>
<td>• &lt;12&lt;br&gt; • ≥12</td>
<td>1.05b (-0.56 to 2.67)&lt;br&gt;1.27b (-1.14 to 3.68)</td>
<td>0.80c (0.43 to 1.49)&lt;br&gt;0.93c (0.58 to 1.50)</td>
<td>0.72c (0.28 to 1.82)&lt;br&gt;1.04c (0.54 to 1.99)</td>
</tr>
<tr>
<td>Gyöngyösi et al (2015) 9</td>
<td>2012</td>
<td>12</td>
<td>1252</td>
<td>RCT or cohort</td>
<td>≤14 d</td>
<td>• Median, 6&lt;br&gt; • Range, 3-12</td>
<td>0.96 (-0.2 to 2.1)&lt;br&gt;0.70 p=0.499</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

CV: cardiovascular; LVEF: left ventricular ejection fraction; NR: not reported; RCT: randomized controlled trial.

a Mantel-Haenszel odds ratio (95% confidence interval).
b As measured by magnetic resonance imaging.
c Relative risk (95% confidence interval).

**Randomized Controlled Trials**

Key studies, including RCTs with more than 100 patients per arm, are described next.

**REPAIR-AMI Trial**

REPAIR-AMI was a double-blinded trial that infused bone marrow–derived progenitor cells or a placebo control infusion of the patient’s own serum; it enrolled 204 patients from 17 centers in Germany and Switzerland who had acute ST-segment elevation myocardial infarction and met strict inclusion criteria.(11,12) At 12-month follow-up, there were statistically significant decreases in the progenitor cell group compared with the control group for MI (0...
vs 6, p<0.03) and revascularization (22 vs 37, p<0.03), as well as for the composite outcome of death, MI, and revascularization (24 vs 42, p<0.009), all respectively. Two-year clinical outcomes from the REPAIR-AMI trial, performed according to a study protocol amendment filed in 2006, were reported in 2010. (11,13) Eleven deaths occurred during the 2-year follow-up, 8 in the placebo group and 3 in the progenitor cell group. There was a significant reduction in MI (0% vs 7%), and a trend toward a reduction in rehospitalizations for heart failure (1% vs 5%) and revascularization (25% vs 37%) in the active treatment group. Analysis of combined events (all combined events included infarction) showed significant improvement with progenitor cell therapy after AMI. There was no increase in ventricular arrhythmia or syncope, stroke, or cancer. It was noted that investigators and patients were unblinded at 12-month follow-up. Also, the REPAIR-AMI trial was not powered to definitively determine whether administration of progenitor cells reduces mortality and morbidity after AMI; the relatively small sample size might have limited the detection of infrequent safety events. Thus, this analysis should be viewed as hypothesis-generating, providing the rationale to design a larger trial addressing clinical end points.

**HEBE Trial**
In 2011, Hirsch et al reported a multicenter RCT of bone marrow or peripheral blood mononuclear cell infusion compared with standard therapy in 200 patients with AMI treated with primary percutaneous coronary intervention (PCI). (14) Mononuclear cells were delivered 3 to 8 days after AMI. Blinded assessment of the primary end point (the percentage of dysfunctional LV segments that had improved segmental wall thickening at 4 months) found no significant difference between the treatment groups (38.5% for bone marrow, 36.8% for peripheral blood) and controls (42.4%). There was no significant difference between the groups in LVEF; change in LV volumes, mass, or infarct size; or rates of clinical events. At 4 months, a similar percentage of patients had New York Heart Association (NYHA) class II or higher heart failure (19% for bone marrow, 20% for peripheral blood, 18% for controls).

**Section Summary: Treatment With Progenitor Cells for Acute Cardiac Ischemia**
The evidence on progenitor cell therapy for patients with MI includes 2 RCTs (200 patients), numerous small RCTs, and meta-analyses of these RCTs. Studies varied by types of cell used and methods and timing of delivery. Most studies reported outcomes for LVEF and/or myocardial perfusion at 3 to 6 months. These studies generally reported small-to-modest improvements in these intermediate outcomes. Limited evidence on clinical outcomes has suggested that there may be benefits in improving LVEF, reducing recurrent MI, decreasing the need for further revascularization, and perhaps even decreasing mortality, although a recent, large, IPD meta-analysis reported no improvement in these outcomes. No single adequately powered trial has reported benefits in clinical outcomes, such as mortality, adverse cardiac outcomes, exercise capacity, or 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.
TREATMENT WITH PROGENITOR CELLS FOR CHRONIC CARDIAC ISCHEMIA

Systematic Reviews
In 2014, Fisher et al published a Cochrane review of autologous stem cell therapy for chronic ischemic heart disease and congestive heart failure. Literature was searched through March 2013, and 23 RCTs (total N=1255 patients) were included. The overall quality of the evidence was considered low because there were few events of interest (deaths, hospital readmissions). In long-term (≥12 months), but not short-term (<12 months), follow-up, there were statistically significant reductions in all-cause mortality (RR=0.3; 95% CI, 0.1 to 0.5; p<0.001; I²=0%) and rehospitalizations due to heart failure (RR=0.3; 95% CI, 0.1 to 0.9; p=0.039; I²=0%) in patients who received stem cell infusion compared with controls (no stem cell infusion). Statistically significant improvements in LVEF and in NYHA classification in stem cell groups were observed at both 6 months and 1 year or later. Evidence was considered of moderate quality for these outcomes, but statistical heterogeneity was moderate to substantial. Similar results were achieved in 2014 meta-analyses conducted by Xu et al and by Xiao et al. Additional research in larger studies is required to confirm these results.

Nonrandomized Controlled Trials

STAR-Heart Trial
The largest study on stem cell therapy for chronic heart failure due to ischemic cardiomyopathy is the 2010 STAR-Heart trial; it was a nonrandomized open-label study with 391 patients with chronic heart failure. In this trial, 191 patients received intracoronary BMC therapy, and 200 patients who did not accept the treatment but agreed to undergo follow-up testing served as controls. Mean time between PCI for infarction and admission to the tertiary clinic was 8.5 years. For BMC therapy, mononuclear cells were isolated and identified (included CD34-positive cells, AC133-positive cells, CD45-/CD14-negative cells). Cells were infused directly into the infarct-related artery. At up to 5 years after intracoronary BMC therapy, there was significant improvement in hemodynamics (LVEF, cardiac index), exercise capacity (NYHA classification), oxygen uptake, and LV contractility compared with controls. There also was a significant decrease in long-term mortality in the BMC-treated patients (0.75% per year) compared with the control group (3.68% per year, p<0.01). However, the study is limited by the potential for selection bias due to patient self-selection into treatment groups. For example, there was a 7% difference in baseline ejection fraction between groups, suggesting that the groups were not comparable on important clinical characteristics at baseline. Additionally, lack of blinding raises the possibility of bias in patient-reported outcomes such as NYHA class.

Section Summary: Treatment With Progenitor Cells for Chronic Cardiac Ischemia
The evidence on progenitor cell therapy for chronic ischemia includes a nonrandomized comparative trial and systematic reviews of smaller RCTs. The studies included in the meta-analyses reported only a small number of clinical
outcome events, too few for meaningful analysis. Results of the STAR-Heart nonrandomized trial are encouraging but not definitive, especially the mortality outcomes, because this is the first controlled trial to report a significant mortality benefit for progenitor cell treatment. Other clinical outcomes (eg, change in NYHA class) are not reported with sufficient methodologic rigor to permit conclusions.

PROGENITOR CELL THERAPY FOR REFRACTORY ANGINA
Stem cell therapy also is being investigated in patients with intractable angina who are not candidates for revascularization. The evidence includes 2 phase 2 trials from 2009 and 2011 that compared infusion of stem cells from peripheral blood or bone marrow to placebo,(19,20) and the following 2016 report from a phase 3 trial.

RENEW Trial
In 2016, Povsic et al reported on the industry-sponsored Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells (RENEW) trial.(21) This 3-arm multicenter trial compared outcomes from intramyocardial administration of autologous CD34+ cells using exercise capacity at 3, 6, or 12 months. Patients underwent cell mobilization with G-CSF for 4 days followed by apheresis. The peripheral cell product was shipped to central processing facility (Progenitor Cell Therapy) for selection of CD34+ cells. The study was terminated after enrollment of 112 of a planned 444 patients prior to data analysis due to strategic considerations. The progenitor cell group had greater exercise capacity than the standard therapy group, but was no better than the double-blinded placebo group, consistent with a placebo effect. In addition, with only 122 participants, the study was not adequately powered to detect a between-group difference.

Section Summary: Progenitor Cell Therapy for Refractory Angina
Evidence on stem cell therapy for refractory angina includes phase 2 trials and a phase 3 pivotal trial 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. No ongoing phase 3 trials on stem cell therapy for refractory angina were identified (see Table 2).

SUMMARY OF EVIDENCE
For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 randomized controlled trials (RCTs) with 200 patients, numerous small 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 even 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.

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SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS
In 2013, American College of Cardiology Foundation and American Heart Association issued joint guidelines for the management of ST-segment elevation myocardial infarction.(22) Progenitor cell therapy was not recommended.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. 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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<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</td>
<td>3000</td>
<td>May 2018</td>
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<td>NCT01781390a</td>
<td>A Prospective, Double Blind, Randomized, Placebo-controlled Clinical Trial of Intracoronary Infusion of Immunoselected, Bone Marrow-derived Str03 Mesenchymal Precursor Cells (MPC) in the Treatment of Patients With ST-elevation Myocardial Infarction</td>
<td>225</td>
<td>Jun 2018</td>
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<tr>
<td>NCT02032004a</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</td>
<td>1730</td>
<td>Aug 2018</td>
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<tr>
<td>NCT01969890</td>
<td>Phase III Study on STem cELls Mobilization in Acute Myocardial Infarction (STEM-AMI)</td>
<td>1530</td>
<td>Oct 2018</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</td>
<td>200</td>
<td>Dec 2018</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</td>
<td>676</td>
<td>Jan 2022</td>
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<tr>
<td>Unpublished</td>
<td>A Phase II, Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of PROCHYMAL® (Ex Vivo Cultured Adult Human Mesenchymal Stem Cells) Intravenous Infusion Following Acute Myocardial Infarction</td>
<td>220</td>
<td>Aug 2016 (completed)</td>
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**References:**


Billing Coding/Physician Documentation Information
There are no specific CPT codes for this procedure. See considerations section.

Additional Policy Key Words
N/A

Policy Implementation/Update Information
4/1/13 New policy; considered investigational.
8/1/13 No policy statement changes.
8/1/14 No policy statement changes.
8/1/15 No policy statement changes.
8/1/16 No policy statement changes.
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