



BlueCross BlueShield  
of Alabama

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**Name of Policy:**

**Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia**

Policy #: 173  
Category: Surgery

Latest Review Date: May 2018  
Policy Grade: C

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**Background/Definitions:**

*As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.*

*The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:*

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

*Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:*

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

## **Description of Procedure or Service:**

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

## **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 (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 includes 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 antiapoptotic 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 vs. cell proliferation with chronic ischemia. Investigation of the specific factors that are induced by administration of progenitor cells is ongoing.

There also are 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 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 in humans is currently unknown.

### **Policy:**

**Progenitor cell therapy**, including but not limited to skeletal myoblasts or hematopoietic stem cells, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** as a treatment of damaged myocardium.

**Infusion of growth factors** (i.e., granulocyte colony stimulating factor [GCSF]) **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

### **Key Points:**

The most recent literature review was performed through March 6, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable

intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The present evidence review focuses on phase 3 trials with at least 100 patients per arm and systematic reviews of RCTs. 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).

## **Progenitor Cells to Treat 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 RCTs (total N=1641 patients). The meta-analysis of De Jong et al (2014) included 22 RCTs (total N=1513 patients). Thirteen RCTs (1300 patients) appeared in both systematic reviews. Both analyses reported statistically significant increases in LVEF with bone marrow stem-cell 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 the de Jong subgroup analysis, which included only trials with outcomes 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 bone marrow cell 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 bone marrow stem cells does not improve clinical outcome.

A 2015 Cochrane review on stem cell treatment for AMI included 41 trials (total N=2732 patients). 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, re-infarction, and re-hospitalization 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 an individual patient data meta-analysis of 12 RCTs (N=1252), including the REPAIR-AMI [trial \(reviewed below\)](#), using a collaborative, multinational database, ACCRUE (meta-Analysis of Cell-based CaRdiac study; NCT01098591). Eight trials had low risk of bias, and four single-blind (assessor) trials had medium-low risk of bias. Adjusted (for cardiovascular risk factors) random effects meta-analyses showed no effect of cell therapy on the primary [outcomes](#), 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 variation in the time from AMI to cell delivery (median, 6.5 days) and in imaging modality for assessing cardiac function (magnetic resonance imaging [MRI], single-proton emission computed tomography [SPECT], angiography, echocardiography).

Fisher et al (2016) reported the results of a trial sequential analysis using cumulative data obtained from 2 previous Cochrane reviews with updated results to March 2015. The intent of the analysis was to obtain estimates of sample size required for a meta-analysis to detect a significant treatment effect while controlling for random errors due to repeat testing. Thirty-seven AMI trials that assessed bone marrow cells and reported mortality as an outcome were included. Of the 37, 14 reported no deaths. Of 23 trials that observed incidences of mortality in either trial arm, a total of 43 (4.0%) deaths in 1073 patients who received cell therapy compared with 38 (5.0%) deaths in 754 patients who did not. Results showed that there is not enough evidence to detect a significant treatment effect of bone marrow derived cells on mortality and rehospitalization in AMI (relative risk [RR], 0.92; 95% confidence interval [CI], 0.62 to 1.36). Results of the sequential analysis showed that at least 4055 participants would be required to detect a relative reduction in the risk of mortality of 35% in AMI patients. Most of the meta-analyses reported so far have not reached this sample size.

### *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. 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; I<sup>2</sup>=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.

### Randomized Controlled Trials

Key studies, [including phase 3 RCTs with more than 100 patients per arm](#) are described next. [Summaries of trial characteristics and results are in Tables 2 and 3.](#)

### REPAIR-AMI

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 and enrolled 204 patients from 17 centers in Germany and Switzerland who had acute STEMI and met strict inclusion criteria. 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,  $p<0.03$ , both respectively), as well as for the composite outcome of death, MI, and revascularization (24 vs 42,  $p<0.009$ , respectively). Two-year clinical outcomes from the REPAIR-AMI trial, performed according to a study protocol amendment filed in 2006, were reported in 2010. A total of 11 deaths occurred during the 2 year follow-up, eight 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 answer the question of whether administration of progenitor cells can improve mortality and morbidity after AMI.

### HEBE Trial

In 2011, Hirsch et al reported a multicenter, phase 3, RCT that compared bone marrow or peripheral blood mononuclear cell infusion compared with standard therapy in 200 patients with AMI treated with primary percutaneous coronary intervention (PCI). Mononuclear cells were delivered 3 to 8 days after MI. 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 either of the treatment groups (38.5% for bone marrow, 36.8% for peripheral blood) and control (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, there was a similar percentage of patients with New York Heart Association (NYHA) class II or higher heart failure (19% for bone marrow, 20% for peripheral blood, 18% for control).

**Table 1: Summary of Systematic Reviews Assessing Use of Progenitor Cell Therapy to Treat Acute Ischemia**

Study (Year)	Dates	Trials	Patients	Study Design	Mean Time Between Acute Event and Cell Infusion	Trial Duration, mo	Mean Change or % Change in LVEF	Risk of All-Cause Mortality	Risk of CV Mortality
Delewi et al (2014)	1980-Feb 2013	16	1641	RCT	≤1 mo	• Median, 6 • Range, 3-6	2.55% (1.83% to 3.26%) $I^2=84%$	NR	NR
De Jong et al (2014)	Jan 2002-	22	1513	RCT	≤1 mo	• Median, 6	2.10% (0.68%	0.68 <sup>a</sup> (0.36 to	0.73 <sup>a</sup> (0.32 to

	Sep 2013					• Range, 3-60	to 3.52%) $I^2=80\%$	1.31)	1.65)
Fisher et al (2015)	Through Mar 2015	41	2732	RCT	≤14 d	• <12 • ≥12	1.05 <sup>b</sup> (-0.56 to 2.67) 1.27 <sup>b</sup> (-1.14 to 3.68)	0.80 <sup>c</sup> (0.43 to 1.49) 0.93 <sup>c</sup> (0.58 to 1.50)	0.72 <sup>c</sup> (0.28 to 1.82) 1.04 <sup>c</sup> (0.54 to 1.99)
Gyöngyösi et al (2015)		12	1252	RCT or cohort	≤14 d	• Median, 6 • Range, 3-12	0.96 (-0.2 to 2.1)	0.70 p=0.499	NR

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

<sup>a</sup> Mantel-Haenszel odds ratio (95% confidence interval).

<sup>b</sup> As measured by magnetic resonance imaging.

<sup>c</sup> Relative risk (95% confidence interval).

**Table 2. RCT Characteristics of Progenitor Cell Therapy for Acute Ischemia**

Study: Trial	Countries	Sites	Dates	Participants	Interventions	
					Cell Therapies	Comparator
Schächinger et al (2006), REPAIR-AMI (NCT00279175)	Germany, Switzerland	17	2004-2005	Acute ST-elevation MI; successfully re-perfused; LVEF <45%	Intracoronary infusion of BMCs (n=101)	Sham infusion (n=103)
Hirsch et al (2011); HEBE (ISRCTN95796863)	Netherlands	8	2005-2008	ST-segment elevation MI; treated with primary PCI and stent implantation	<ul style="list-style-type: none"> <li>• Intracoronary infusion of autologous mononuclear BMCs (n=69)</li> <li>• Intracoronary infusion of mononuclear peripheral blood cells (n=66)</li> </ul>	Standard of care without sham infusion (n=65)

BMC: bone marrow cell; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention.

**Table 3. RCT Results of Progenitor Cell Therapy for Acute Ischemia**

Study	Mortality, n	Major Adverse Events, n	Rehospitalization for Heart Failure, n	LVEF
			By 1 Year	Mean Change From BL to 4 Months (SD)
Schächinger et al (2006)				
N	204	204	204	187
Cell therapy	6	23	0	5.5 (7.3)
Sham	2	40	3	3.0 (6.5)
TE (95% CI); p	NR; p=0.28	NR; p=0.01	NR; p=0.25	NR; p=0.01
	By 4 Months	Death, MI Revascularization by 4 Months	By 4 Months	Mean Change From BL to 4 Months (SD)

<u>Study</u>	<u>Mortality, n</u>	<u>Major Adverse Events, n</u>	<u>Rehospitalization for Heart Failure, n</u>	<u>LVEF</u>
<u>Hirsch et al (2011)</u>				
<u>N</u>	<u>200</u>	<u>200</u>	<u>200</u>	
<u>BMC therapy</u>	<u>0</u>	<u>4</u>	<u>0</u>	<u>189</u>
<u>PBC therapy</u>	<u>1</u>	<u>9</u>	<u>1</u>	<u>3.8 (7.4)</u>
<u>SOC</u>	<u>0</u>	<u>6</u>	<u>1</u>	<u>4.2 (6.2)</u>
<u>TE (95% CI); p</u>	<u>NR</u>	<u>NR</u>	<u>NR</u>	<u>4.0 (5.8)</u>

BL: baseline; BMC: bone marrow cell; CI: confidence interval; LVEF: left ventricular ejection fraction; NR: not reported; PBC: peripheral blood cell; RCTA: randomized controlled trial; SOC: standard of care; TE: treatment effect.

### Section Summary: Treatment with Progenitor Cells for Acute Cardiac Ischemia

The evidence on progenitor cell therapy for patients with MI includes 2 phase 3 RCTs including more than 100 patients, numerous small, early phase RCTs, and meta-analyses of these RCTs. Studies varied by types of cell used and methods and timing of delivery. Most studies reported outcomes of 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, individual patient data 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 suggests 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.

### Progenitor Cells to Treat Chronic Cardiac Ischemia

Stem cell therapy is also being investigated in patients with chronic ischemic heart disease. The evidence includes systematic reviews, many small, early-phase RCTs, 2 phase 3 RCTs with more than 100 participants, and nonrandomized studies.

### Systematic Reviews

Fisher et al (2016) reported on a systematic review<sup>15</sup> that updated a 2014 Cochrane. In 2016, literature was searched through December 2015, and 38 RCTs (total N=1907) were included. Overall quality of the evidence was considered low because selected studies were small (only 3 included >100 participants) and the number of events was low, leading to a risk of small study bias and spuriously inflated effect sizes. Results of the 2016 Cochrane review are shown in Table 4. While reviewers were unable to detect evidence of publication bias using funnel plots, they noted that of 28 identified ongoing trials, 11 trials with 787 participants, were recorded as having been completed or were due to have been completed in advance of the search date but had no publications. Therefore, publication bias cannot be ruled out. Similar results were reported 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.



**Table 4. Cochrane Review Results of Stem Cell Therapy for Chronic Ischemic Heart Disease**

<u>Variables</u>	<u>Short-Term<sup>a</sup> Mortality</u>	<u>Long-Term<sup>b</sup> Mortality</u>	<u>Long-Term<sup>b</sup> Rehospitalization</u>	<u>Long-Term<sup>b</sup> MACE</u>	<u>Short-Term<sup>a</sup> NYHA Classification</u>	<u>Short-Term<sup>a</sup> LVEF (%)<sup>c</sup></u>
<u>N</u>	<u>1637</u>	<u>1010</u>	<u>495</u>	<u>201</u>	<u>658</u>	<u>352</u>
<u>PE (95% CI); p value</u>	<u>0.48 (0.26 to 0.87); 0.02</u>	<u>0.38 (0.25 to 0.58); &lt;0.001</u>	<u>0.62 (0.36 to 1.04); 0.07</u>	<u>0.68 (0.41 to 1.12); 0.13</u>	<u>-0.42 (-0.84 to -0.00); 0.05</u>	<u>3.01 (-0.05 to 6.07); 0.054</u>
<u>I<sup>2</sup> (p)</u>	<u>0% (0.76)</u>	<u>0% (0.97)</u>	<u>0% (0.70)</u>	<u>0% (0.80)</u>	<u>97% (&lt;0.001)</u>	<u>59% (0.01)</u>

Adapted from Fisher et al (2016).

CI: confidence interval; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; NYHA: New York Heart Association; PE: pooled effect.

a Short-term: <12 months.

b Long-term: >12 months.

c Measured by magnetic resonance imaging.

Fisher et al (2016) reported the results of a sequential trial analysis using cumulative data obtained from 2 previous Cochrane reviews with updated results to March 2015. The intent of the analysis to obtain estimates of sample size required for a meta-analysis to detect a significant treatment effect while controlling for random errors due to repeat testing. A total of 22 trials that included all-cause mortality were included. Six trials reported no deaths, while the remaining 16 trials reported 25 (5.6%) deaths in 444 patients who received cells compared with 50 (15.9%) deaths in 315 patients who did not. Meta-analysis of the pooled data revealed a significant reduction in mortality associated with cell therapy in patients with heart failure (RR=0.42; 95% CI; 0.27 to 0.64; p<0.001).

#### Randomized Controlled Trials

Two phase 3 RCTs with more than 100 participants were identified. Trial characteristics and results are shown in Tables 5 and 6. Bartunek et al (2017) reported the results of a well-conducted double-blind, randomized trial in which 271 patients with NYHA class II or greater symptomatic heart failure (LVEF ≤35%) were randomized to bone marrow-derived mesenchymal cardiopoietic cells (n=120) or sham (n=151). The primary end point was Finkelstein–Schoenfeld hierarchical composite (all-cause mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, 6-minute walk distance, left ventricular end-systolic volume, and ejection fraction) at 39 weeks. Sixteen patients who died and 3 who withdrew consent after randomization were not included in the analysis. Also, 19 patients whose cell product did not meet release criteria were excluded from analysis in the cardiopoietic cell group. The probability that the treatment group had a better outcome on the composite primary outcome was 0.54 (a value >0.5 favors active treatment; 95% CI, 0.47 to 0.61; p=0.27). Exploratory subgroup analysis reported treatment benefit in patients with baseline left ventricular end-diastolic volume of 200 to 370 mL (60% of patients) (0.61; 95% CI, 0.52 to 0.70; p=0.015). There was no statistical difference in serious adverse events between the two treatment arms. One (0.9%) cardiopoietic cell patient and 9 (5.4%) sham patients experienced aborted or sudden cardiac death.

Pokushalov et al (2010) reported on the results of an RCT of intramyocardial injections of autologous bone marrow mononuclear cells (n=55) compared with optimal medical management (n=54) in patients who had chronic, ischemic heart failure. The trial appears to have been

conducted in Russia; dates of study conduct were not reported. Power calculations were not reported, and it is not clear if the trial was registered. Comparative treatment effects were not calculated for many outcomes. Characteristics and results are shown in Tables 5 and 6. The RCT reported statistically significant improvements in mortality rates at 12 months for cell therapy (11%) vs medical therapy (39%) favoring medical therapy ( $p < 0.001$ ).

**Table 5. RCT Characteristics of Progenitor Cell Therapy for Chronic Ischemic Heart Disease**

					<b>Interventions</b>	
<b>Study: Trial</b>	<b>Countries</b>	<b>Sites</b>	<b>Dates</b>	<b>Participants</b>	<b>Cell Therapy</b>	<b>Comparator</b>
<u>Bartunek et al (2017); CHART-1 (NCT01768702)</u>	<u>Multination al<sup>a</sup></u>	<u>39</u>	<u>2012-2015</u>	<u>LVEF &lt;35%, NYHA class &gt;II on guidelines-directed therapy</u>	<u>Cardiopoietic cells (n=157)</u>	<u>Sham (n=158)</u>
<u>Pokushalov et al (2010)</u>	<u>Russia</u>	<u>NR</u>	<u>NR</u>	<u>LVEF &lt;35%, end-stage, chronic heart failure, on optimal medical therapy, not eligible for revascularization</u>	<u>Bone marrow cells (n=55)</u>	<u>Medical management, no sham (n=54)</u>

LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association

<sup>a</sup> Belgium, Bulgaria, Hungary, Ireland, Israel, Italy, Poland, Serbia, Spain, Sweden, Switzerland, and United Kingdom.

**Table 6. RCT Results of Progenitor Cell Therapy for Chronic Ischemic Heart Disease**

<b>Study</b>	<b>Mortality, n (%)</b>	<b>Change in Heart Failure, n (%)</b>	<b>MLHFQ Score, n (%)</b>	<b>6-Minute Walk</b>	<b>LVEF</b>
	<b>At 39 Weeks</b>	<b>Worsening; &gt;1 Event Through 39 Weeks</b>	<b>&gt;10-point Improvement From BL to 39 Weeks</b>	<b>&gt;40 m Improvement From BL to 39 Weeks, n (%)</b>	<b>&gt;4% Improvement From BL to 39 Weeks, n (%)</b>
<b>Bartunek et al (2017)</b>					
<u>N</u>	<u>271</u>	<u>271</u>	<u>244</u>	<u>239</u>	<u>226</u>
<u>Cell therapy</u>	<u>11 (9%)</u>	<u>20 (17%)</u>	<u>64 (59%)</u>	<u>50 (46%)</u>	<u>69 (68%)</u>
<u>Sham</u>	<u>12 (8%)</u>	<u>23 (15%)</u>	<u>66 (49%)</u>	<u>40 (31%)</u>	<u>82 (66%)</u>
<u>TE (95% CI); p</u>	<u>HR=1.2 (0.5 to 2.7); 0.70</u>	<u>Odds<sup>a</sup>=1.03 (0.9 to 1.2); 0.72</u>	<u>Odds<sup>a</sup>=0.8 (0.7 to 1.0); 0.12</u>	<u>Odds<sup>a</sup>=0.8 (0.7 to 1.0); 0.07</u>	<u>Odds<sup>a</sup>=1.0 (0.8 to 1.2); 0.73</u>
	<b>At 12 Months</b>	<b>Improvement in NYHA Class by 1 Class at 3 Months</b>		<b>Mean Distance Walked at 12 Months (SD), m</b>	<b>Mean at 3 Months (SD)</b>
<b>Pokushalov et al (2010)</b>					
<u>N</u>	<u>109</u>	<u>107</u>		<u>NR</u>	<u>107</u>
<u>Cell therapy</u>	<u>6 (11%)</u>	<u>25 (46%)</u>		<u>359 (69)</u>	<u>28 (6)</u>
<u>Sham</u>	<u>21 (39%)</u>	<u>4 (8%)</u>		<u>196 (42)</u>	<u>27 (6)</u>
<u>TE (95% CI); p</u>	<u>&lt;0.001</u>	<u>NR</u>		<u>0.03</u>	<u>NR</u>

BL: baseline; HR: hazard ratio; LVEF, left ventricular ejection fraction; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NR: not reported; RR: relative risk; TE: treatment effect.

<sup>a</sup>Mann-Whitney odds for worse outcome in cell therapy vs sham for ordered categories; note, not all categories are shown in this table. Values <1.0 favor cell therapy treatment.

## Nonrandomized Controlled Trials

### *STAR-Heart Trial*

The STAR-Heart trial evaluated stem cell therapy for chronic heart failure due to ischemic cardiomyopathy. This nonrandomized open-label study, reported by Stauer et al (2010), evaluated 391 patients with chronic heart failure. In this trial, 191 patients received intracoronary bone marrow cell (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 five 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 trial 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 the two 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 RCTs, systematic reviews of RCTs and a nonrandomized comparative trial. The studies included in the meta-analyses were generally early phase, small (<100 participants) trials; they only reported on a small number of clinical outcome events. The findings from early-phase 2 trials need to be corroborated in a larger phase 3 trial. One well-conducted, phase 3 trial failed to demonstrate superiority for cell therapy for the primary outcome that included death, worsening heart failure, and other multiple events. The nonrandomized STAR-Heart trial showed a mortality benefit as well as a favorable hemodynamic effect but the lack of randomization limits interpretation due to the concern of selection bias and differences in known and unknown prognostic variables at baseline between arms. 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.

### **Progenitor Cell Therapy to Treat Refractory Angina**

Stem-cell therapy also is being investigated in patients with intractable angina who are not candidates for revascularization. The evidence includes a systematic review, 4 trials from 2007 through 2014 with fewer than 100 patients, 2 phase ½ trials with more than 100 patients, and 1 phase 3 trial with more than 100 participants, which is discussed more in the section on RCTs.

### Systematic Reviews

Khan et al (2016) reported on the results of a systematic review of RCTs evaluating cell therapy in patients with refractory angina who were ineligible for coronary revascularization. The risk of

bias in the included studies was rated as low. All selected randomized trials were placebo-controlled; 5 RCTs were blinded and in one blinding was not reported. The systematic review characteristics and results are shown in Tables 7 and 8. The trials varied in durations of follow-up but appear to have been pooled regardless of the timing of the outcome in the analysis. Although there was a beneficial effect of cell therapy on frequency of angina in the pooled analysis, there was significant heterogeneity for the angina outcome, which was attributed to 1 RCT. With removal of this RCT, there was an attenuation of the effect (mean difference, -3.38; 95% CI, -6.56 to 0.19).

**Table 7. Systematic Review Characteristics of Progenitor Cell Therapy for Refractory Angina**

<u>Study</u>	<u>Dates</u>	<u>Trials</u>	<u>Participants</u>	<u>N (Range)</u>	<u>Design</u>	<u>Length of FU</u>
<u>Khan et al (2016)</u>	<u>Up to Sep 2015</u>	<u>6</u>	<u>Refractory angina who were ineligible for coronary revascularization</u>	<u>353 (24-112)</u>	<u>RCT</u>	<u>6 mo to 2 y</u>

FU: follow-up; RCT: randomized controlled trial

**Table 8. Systematic Review Results of Progenitor Cell Therapy for Refractory Angina**

<u>Study</u>	<u>Frequency of Angina</u>	<u>CCS Angina Class</u>	<u>MACE</u>	<u>Mortality</u>	<u>QOL</u>
<u>Khan et al (2016)</u>					
<u>Total N</u>	<u>271</u>	<u>210</u>	<u>NR</u>	<u>NR</u>	<u>NR</u>
<u>PE (95% CI); p value</u>	<u>MD = -7.8 (-15.2 to -0.41); 0.04</u>	<u>MD = -0.58 (-1.00 to -0.16); 0.007</u>	<u>OR=0.49 (0.25 to 0.98); 0.04</u>	<u>NR</u>	<u>NR</u>
<u>I<sup>2</sup> (p)</u>	<u>90% (&lt;0.001)</u>	<u>0% (0.67)</u>	<u>0% (NR)</u>	<u>NR</u>	<u>NR</u>

CCS: Canadian Cardiovascular Society; CI: confidence interval; MACE: major adverse cardiac events; MD: mean difference; OR: odds ratio; PE: pooled effect; QOL: quality of life.

### Randomized Controlled Trials

One phase 3 trial of cell therapy in patients with refractory angina who were ineligible for coronary revascularization including more than 100 participants has been reported. Characteristics and results are shown in Tables 9 and 10.

### 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. 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.

**Table 9. RCT Characteristics of Progenitor Cell Therapy for Refractory Angina**

<u>Study; Trial</u>	<u>Countries</u>	<u>Sites</u>	<u>Dates</u>	<u>Participants</u>	<u>Interventions</u>	
					<u>Cell Therapy</u>	<u>Comparator</u>
<u>Povsic et al (2016); RENEW (NCT01508910)</u>	<u>U.S.</u>	<u>41</u>	<u>2012-2013</u>	<u>CCS class III/IV angina, LVEF &gt;25%, on maximally tolerated drug therapy, not eligible for revascularization</u>	<u>Autologous CD34-positive (G-CSF stem cell mobilization, apheresis, and IM CD34-positive injection) (n=54)</u>	<ul style="list-style-type: none"> <li>• <u>Standard of care: no additional intervention, not blinded (n=28)</u></li> <li>• <u>Active control: G-CSF stem cell mobilization, apheresis, and IM placebo injection (n=27)</u></li> </ul>

CCS: Canadian Cardiovascular Society; G-CSF: granulocyte colony stimulating factor; IM: intramyocardial; LVEF: left ventricular ejection fraction.

**Table 10. RCT Results of Progenitor Cell Therapy for Refractory Angina**

<u>Study</u>	<u>Angina Frequency</u>	<u>Exercise Time, s</u>	<u>MACE, n (%)</u>	<u>Death, n (%)</u>	<u>QOL</u>
	<u>Mean Episodes/Week at 12 Months (SD)</u>	<u>Mean Change From BL to 12 Months (SD)</u>	<u>At 24 Months</u>	<u>At 24 Months</u>	
<u>Povsic et al (2016)</u>					
<u>N</u>	<u>84</u>	<u>84</u>	<u>106</u>	<u>106</u>	<u>NR</u>
<u>CT</u>	<u>3.8 (6.2)</u>	<u>109 (194)</u>	<u>23 (46%)</u>	<u>2 (4%)</u>	
<u>SOC</u>	<u>NR</u>	<u>NR</u>	<u>19 (68%)</u>	<u>2 (7%)</u>	
<u>AC</u>	<u>2.7 (4.6)</u>	<u>90 (185)</u>	<u>12 (43%)</u>	<u>3 (11%)</u>	
<u>TE for CT vs AC (95% CI); p</u>	<u>RR=1.02 (NR); 0.95</u>	<u>20.4 (-68.9 to 109.6); 0.65</u>	<u>NR</u>	<u>NR</u>	
<u>TE for CT vs SOC (95% CI); p</u>	<u>NR</u>	<u>NR</u>	<u>NR</u>	<u>NR</u>	

AC: active control; BL: baseline; CT: cell therapy; MACE: major adverse cardiac events; QOL: quality of life; SOC: standard of care; RR: relative risk; SOC: standard of care; TE: treatment effect.

### Section Summary: Progenitor Cell Therapy for Refractory Angina

Evidence on stem-cell therapy for refractory angina includes early-phase trials, as well as 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.

### Summary of Evidence

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 phase 3 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, reducing recurrent myocardial infarction, decreasing the need for further revascularization, and perhaps even decreasing mortality, although a recent, large meta-analysis reported no improvement in mortality. 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 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. 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.

### **Practice Guidelines and Position Statements**

American College of Cardiology Foundation/American Heart Association

In 2013, ACCF and AHA issued joint guidelines for the management of STEMI. Progenitor cell therapy is not recommended.

### **U.S. Preventive Services Task Force Recommendations**

Not applicable

### **Key Words:**

Autologous cell transplantation, BioHeart, autologous skeletal myoblasts, cardiovascular disease, congestive heart failure, coronary disease, heart disease, myoblast transplantation, myocardial infarction, allogeneic human mesenchymal stem cell, hMSC, Prochymal, progenitor cells, post-infarct necrosis, regeneration, stem cells, transfusion, Athersys, Multistem®, Osiris, Provacel®, infusion of growth factors, intramyocardial stem cell injection, MyoCell®, Ixmyelocel-T

### **Approved by Governing Bodies:**

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 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).<sup>3</sup> 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.

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 for mesenchymal and macrophage lineages might enhance potency. Vericel has received RMAT designation for Ixmyelocel-T.

MultiStem® (Athersys) is an allogeneic bone marrow–derived adherent adult stem cell product.

CardiAMPTM 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 CardiAMPTM.

### **Benefit Application:**

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

### **Current Coding:**

There are no specific CPT codes for this procedure.

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### **Policy History:**

Medical Policy Group, June 2004

Medical Policy Administration Committee, July 2004

Available for comment July 12-August 25, 2004

Medical Policy Group, June 2005 (1)

Medical Policy Group, June 2006 (1)

Medical Policy Group, January 2007 (2)

Medical Policy Group, January 2008 (1)

Medical Policy Group, February 2009 (4)

Medical Policy Group, February 2010 (1)

Medical Policy Group, July 2010 (1): Medical policy updated, coverage remains unchanged, name change

Medical Policy Administration Committee, July 2010

Medical Policy Group, July 2011 (1): Update to Key Points and References

Medical Policy Group July 2012 (1): Update to 2012 Key Points and References

Medical Policy Panel, June 2013

Medical Policy Group, June 2013 (3): 2013 Update to Key Points and References; no change in policy statement; Removed information concerning MyoCell study (2006) which was never completed.

Medical Policy Panel

Medical Policy Group, June 2014 (3): 2014 Updates to Key Points, Key Words, Governing Bodies & References; no change in policy statement

Medical Policy Panel, June 2015

Medical Policy Group, June 2015 (4): Updates to Key Points and References. No change in policy statement.

Medical Policy Panel, December 2016.

Medical Policy Group, January 2017 (4): Updates to Description, Key Points, Key Words, Approved Governing Bodies, and References. No change in policy statement.

Medical Policy Panel, August 2017

Medical Policy Group, August 2017 (4): Updates to Key Points, Governing Bodies, Key Words and references. No change to policy statement.

Medical Policy Panel, May 2018

Medical Policy Group, May 2018 (4): Updates to Key Points, Approved by Governing Bodies and References. No change to Policy statement.

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*This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date*

*hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.*