

**DRAFT Medical Coverage Policy | Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia**



**EFFECTIVE DATE:**  
**POLICY LAST UPDATED:**

**OVERVIEW**

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.

**MEDICAL CRITERIA**

Not applicable

**PRIOR AUTHORIZATION**

Not applicable

**POLICY STATEMENT**

Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic cells, is considered not medically necessary as a treatment of damaged myocardium

Infusion of growth factors (ie, granulocyte colony stimulating factor) is considered not medically necessary as a technique to increase the numbers of circulating hematopoietic cells as treatment of damaged myocardium

These services are not medically necessary as 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

**COVERAGE**

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessity benefits/coverage.

**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 unable to 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 actually 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 suggests that injected stem cells secrete cytokines with antiapoptotic and proangiogenesis 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 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 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.

## **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 Provacel®; 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 a ischemic stroke.

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 metaanalyses 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.

## **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.<sup>22</sup> Progenitor cell therapy was not recommended.

## **CODING**

There are no specific codes for this procedure, either describing the laboratory component of processing the harvested autologous cells or for the implantation procedure. Claims should be filed with an unlisted CPT code

## **RELATED POLICIES**

Not applicable

## **PUBLISHED**

Provider Update XXXX 2017

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