



# MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

## Medical Policy

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

### Table of Contents

- [Policy: Commercial](#)
- [Policy: Medicare](#)
- [Authorization Information](#)
- [Coding Information](#)
- [Description](#)
- [Policy History](#)
- [Information Pertaining to All Policies](#)
- [References](#)

### Policy Number: 652

BCBSA Reference Number: 2.02.18 (For Plan internal use only)

NCD/LCD: NA

### Related Policies

- Orthopedic Applications of Stem-Cell Therapy, #[254](#)
- Stem-cell Therapy for Peripheral Arterial Disease, #[348](#)

### Policy

## Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

Progenitor cell therapy, including but not limited to, skeletal myoblasts or hematopoietic stem cells, is **INVESTIGATIONAL** as a treatment of damaged myocardium.

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

### Prior Authorization Information

#### Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

#### Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is <b>not</b> a covered service.
Commercial PPO and Indemnity	This is <b>not</b> a covered service.

Medicare HMO Blue <sup>SM</sup>	This is <b>not</b> a covered service.
Medicare PPO Blue <sup>SM</sup>	This is <b>not</b> a covered service.

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

## CPT Codes

There is no specific CPT code for this service.

## Description

### Ischemia

Ischemia is the most common cause of cardiovascular disease and myocardial damage in the developed world. Despite impressive advances in treatment, ischemic heart disease is still associated with high morbidity and mortality. According to the American Heart Association, coronary heart disease has a prevalence of 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people.<sup>1</sup> For all age strata, the incidence of myocardial infarction is higher in Black males than in Black females, White males, and White females. Heart failure has the highest prevalence among Black males (3.8%) followed by Black females (3.3%), White males (2.9%), Hispanic males (1.8%), Hispanic and White females (both 1.6%), Asian males (1.4%) and Asian females (0.5%). Age-adjusted death rates per 100,000 individuals with coronary heart disease and heart failure are higher for Black males and females than their counterparts of other races.

### Treatment

Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments do not reverse existing heart muscle damage.<sup>2</sup> 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, adult testis pluripotent stem cells, mesothelial cells, adipose-derived stromal cells, embryonic cells, induced pluripotent stem cells, and bone marrow mesenchymal stem cells, all of which can differentiate into cardiomyocytes and vascular endothelial cells for regenerative medicine advanced therapy (RMAT).<sup>3</sup> The RMAT designation may be given if: (1) the drug is a regenerative medicine therapy (ie, a cell therapy), therapeutic tissue engineering product, human cell and tissue product, or any combination product; (2) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and (3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs.

## Summary

### Description

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.

### Summary of Evidence

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 phase 3 RCTs, numerous small, early-phase RCTs, and meta-analyses of these RCTs. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and

hospitalizations. Limited evidence on clinical outcomes has suggested there may be benefits from improving LVEF, reducing recurrent MI, decreasing the need for further revascularization, and perhaps decreasing mortality, although, a recent, large, individual patient data meta-analysis reported no improvement in these outcomes. No adequately powered trial has reported benefits in clinical outcomes (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 that the technology results in an improvement in the net health outcome.

For individuals who have chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes 1 phase 3 RCT with more than 100 participants, 2 phase 2 RCTs with more than 100 participants, systematic reviews of smaller, early-phase RCTs, and a nonrandomized comparative trial. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. The studies included in the meta-analyses have reported only on a small number of clinical outcome events. Two phase 2 RCTs (CONCERT-HF and ixCELL-DCM) found significant benefit on heart failure-related death and other cardiac events with cell therapy compared to placebo. A well-conducted phase 3 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 that the technology results in an improvement in the net health outcome.

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

## Policy History

Date	Action
7/2023	Annual policy review. Reference added. Policy statements unchanged.
6/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
7/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2018	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
9/2017	Annual policy review. New references added.
1/2017	Annual policy review. New references added.
8/2015	Annual policy review. New references added.
9/2014	Annual policy review. New references added.
8/2013	Annual policy review. New references added.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
2/2012	Annual policy review. No changes to policy statements.

4/2011	Reviewed - Medical Policy Group - Cardiology and Pulmonology. No changes to policy statements.
9/2010	Annual policy review. Changes to policy statements.
9/2009	Annual policy review. No changes to policy statements.
4/2009	Reviewed - Medical Policy Group - Cardiology and Pulmonology. No changes to policy statements.
9/2008	Annual policy review. No changes to policy statements.
8/2007	Annual policy review. Changes to policy statements.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

## References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*. Feb 21 2023; 147(8): e93-e621. PMID 36695182
2. Lee MS, Makkar RR. Stem-cell transplantation in myocardial infarction: a status report. *Ann Intern Med*. May 04 2004; 140(9): 729-37. PMID 15126257
3. U.S. Food and Drug Administration. Regenerative Medicine Advanced Therapy Designation. 2023; <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm>. Accessed March 13, 2023.
4. Delewi R, Hirsch A, Tijssen JG, et al. Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. *Eur Heart J*. Apr 2014; 35(15): 989-98. PMID 24026778
5. de Jong R, Houtgraaf JH, Samiei S, et al. Intracoronary stem cell infusion after acute myocardial infarction: a meta-analysis and update on clinical trials. *Circ Cardiovasc Interv*. Apr 2014; 7(2): 156-67. PMID 24668227
6. Fisher SA, Zhang H, Doree C, et al. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. Sep 30 2015; 2015(9): CD006536. PMID 26419913
7. Gyöngyösi M, Wojakowski W, Lemarchand P, et al. Meta-Analysis of Cell-based Cardiac Stem Cell Therapy (ACCRUE) in patients with acute myocardial infarction based on individual patient data. *Circ Res*. Apr 10 2015; 116(8): 1346-60. PMID 25700037
8. Fisher SA, Doree C, Taggart DP, et al. Cell therapy for heart disease: Trial sequential analyses of two Cochrane reviews. *Clin Pharmacol Ther*. Jul 2016; 100(1): 88-101. PMID 26818743
9. Lalu MM, Mazzarello S, Zlepzig J, et al. Safety and Efficacy of Adult Stem Cell Therapy for Acute Myocardial Infarction and Ischemic Heart Failure (SafeCell Heart): A Systematic Review and Meta-Analysis. *Stem Cells Transl Med*. Dec 2018; 7(12): 857-866. PMID 30255989
10. Moazzami K, Roohi A, Moazzami B. Granulocyte colony stimulating factor therapy for acute myocardial infarction. *Cochrane Database Syst Rev*. May 31 2013; 2013(5): CD008844. PMID 23728682
11. Schächinger V, Erbs S, Elsässer A, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. *Eur Heart J*. Dec 2006; 27(23): 2775-83. PMID 17098754
12. Schächinger V, Erbs S, Elsässer A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med*. Sep 21 2006; 355(12): 1210-21. PMID 16990384
13. Assmus B, Rolf A, Erbs S, et al. Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. *Circ Heart Fail*. Jan 2010; 3(1): 89-96. PMID 19996415
14. Hirsch A, Nijveldt R, van der Vleuten PA, et al. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction

- treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. *Eur Heart J*. Jul 2011; 32(14): 1736-47. PMID 21148540
15. Fisher SA, Doree C, Mathur A, et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. Dec 24 2016; 12(12): CD007888. PMID 28012165
  16. Fisher SA, Brunskill SJ, Doree C, et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. Apr 29 2014; (4): CD007888. PMID 24777540
  17. Xu R, Ding S, Zhao Y, et al. Autologous transplantation of bone marrow/blood-derived cells for chronic ischemic heart disease: a systematic review and meta-analysis. *Can J Cardiol*. Nov 2014; 30(11): 1370-7. PMID 24726092
  18. Xiao C, Zhou S, Liu Y, et al. Efficacy and safety of bone marrow cell transplantation for chronic ischemic heart disease: a meta-analysis. *Med Sci Monit*. Oct 01 2014; 20: 1768-77. PMID 25270584
  19. Bolli R, Mitrani RD, Hare JM, et al. A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRNC ONCERT-HF trial. *Eur J Heart Fail*. Apr 2021; 23(4): 661-674. PMID 33811444
  20. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial. *Eur Heart J*. Mar 01 2017; 38(9): 648-660. PMID 28025189
  21. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic stem cell therapy in ischaemic heart failure: long-term clinical outcomes. *ESC Heart Fail*. Dec 2020; 7(6): 3345-3354. PMID 33094909
  22. Patel AN, Henry TD, Quyyumi AA, et al. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. *Lancet*. Jun 11 2016; 387(10036): 2412-21. PMID 27059887
  23. Pokushalov E, Romanov A, Chernyavsky A, et al. Efficiency of intramyocardial injections of autologous bone marrow mononuclear cells in patients with ischemic heart failure: a randomized study. *J Cardiovasc Transl Res*. Apr 2010; 3(2): 160-8. PMID 20560030
  24. Strauer BE, Yousef M, Schannwell CM. The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heart failure: the STAR-heart study. *Eur J Heart Fail*. Jul 2010; 12(7): 721-9. PMID 20576835
  25. Khan AR, Farid TA, Pathan A, et al. Impact of Cell Therapy on Myocardial Perfusion and Cardiovascular Outcomes in Patients With Angina Refractory to Medical Therapy: A Systematic Review and Meta-Analysis. *Circ Res*. Mar 18 2016; 118(6): 984-93. PMID 26838794
  26. van Ramshorst J, Bax JJ, Beeres SL, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. *JAMA*. May 20 2009; 301(19): 1997-2004. PMID 19454638
  27. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation*. Jun 26 2007; 115(25): 3165-72. PMID 17562958
  28. Tse HF, Thambar S, Kwong YL, et al. Prospective randomized trial of direct endomyocardial implantation of bone marrow cells for treatment of severe coronary artery diseases (PROTECT-CAD trial). *Eur Heart J*. Dec 2007; 28(24): 2998-3005. PMID 17984132
  29. Jimenez-Quevedo P, Gonzalez-Ferrer JJ, Sabate M, et al. Selected CD133+ progenitor cells to promote angiogenesis in patients with refractory angina: final results of the PROGENITOR randomized trial. *Circ Res*. Nov 07 2014; 115(11): 950-60. PMID 25231095
  30. Wang S, Cui J, Peng W, et al. Intracoronary autologous CD34+ stem cell therapy for intractable angina. *Cardiology*. 2010; 117(2): 140-7. PMID 20975266
  31. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res*. Aug 05 2011; 109(4): 428-36. PMID 21737787
  32. Povsic TJ, Henry TD, Traverse JH, et al. The RENEW Trial: Efficacy and Safety of Intramyocardial Autologous CD34(+) Cell Administration in Patients With Refractory Angina. *JACC Cardiovasc Interv*. Aug 08 2016; 9(15): 1576-85. PMID 27491607
  33. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College

of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv.* May 2016; 87(6): 1001-19. PMID 26489034

34. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation.* Dec 06 2011; 124(23): e574-651. PMID 22064601
35. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* Jan 29 2013; 61(4): e78-e140. PMID 23256914
36. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* Jan 18 2022; 79(2): e21-e129. PMID 34895950
37. Maddox TM, Januzzi JL, Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* Feb 16 2021; 77(6): 772-810. PMID 33446410
38. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *J Card Fail.* May 2022; 28(5): e1-e167. PMID 35378257