BlueCross BlueShield Arizona

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EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 09/19/22**
SECTION: MEDICINE	**LAST REVIEW DATE: 08/16/22**
	CURRENT EFFECTIVE DATE: 09/19/22
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 3RD QTR 2023	**ARCHIVE DATE:**

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

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.

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; in other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure.

Infusion of growth factors, including granulocyte colony stimulating factor (GCSF), is also being investigated as a treatment for coronary heart disease.

Multiple progenitor cell therapies such as MyoCell® (U.S. Stem Cell, formerly Bioheart), Ixmyelocel-T (Vericel, formerly Aastrom Biosciences), MultiStem® (Athersys), and CardiAMP™ (BioCardia) are being commercially developed, but none has been approved by the U.S. Food and Drug Administration (FDA) so far.

Criteria:

- Progenitor cell therapy as a treatment of damaged myocardium is considered ***experimental or investigational*** when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement outside the investigational setting.

  These therapies include, *but are not limited to:*

  - Skeletal myoblasts
  - Hematopoietic cells

- Infusion of growth factors (i.e., granulocyte colony stimulating factor) as a technique to increase the numbers of circulating hematopoietic cells as treatment of damaged myocardium is considered ***experimental or investigational*** when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

Criteria: (cont.)

2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement outside the investigational setting.

Resources:

Literature reviewed 08/16/22. We do not include marketing materials, poster boards and non-published literature in our review.

1. 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. doi:10.1161/CIRCHEARTFAILURE.108.843243

2. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic stem cell therapy in ischaemic heart failure: long-term clinical outcomes. *ESC Heart Fail*. Oct 23 2020;doi:10.1002/ehf2.13031

3. 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 1 2017;38(9):648-660. doi:10.1093/eurheartj/ehw543

4. 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 CCTRN CONCERT-HF trial. *Eur J Heart Fail*. Apr 2021;23(4):661-674. doi:10.1002/ejhf.2178

5. de Jong R, Houtgraaf JH, Samiei S, Boersma E, Duckers HJ. 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. doi:10.1161/CIRCINTERVENTIONS.113.001009

6. 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. doi:10.1093/eurheartj/eht372

7. Endorsed by the Latin American Society of Interventional C, Pci Writing C, Levine GN, 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. doi:10.1002/ccd.26325

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

Resources: (cont.)

8. Fisher SA, Brunskill SJ, Doree C, Mathur A, Taggart DP, Martin-Rendon E. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev.* Apr 29 2014;(4):CD007888. doi:10.1002/14651858.CD007888.pub2

9. Fisher SA, Doree C, Mathur A, Taggart DP, Martin-Rendon E. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. Dec 24 2016;12:CD007888. doi:10.1002/14651858.CD007888.pub3

10. Fisher SA, Doree C, Taggart DP, Mathur A, Martin-Rendon E. Cell therapy for heart disease: Trial sequential analyses of two Cochrane reviews. *Clin Pharmacol Ther*. Jul 2016;100(1):88-101. doi:10.1002/cpt.344

11. Fisher SA, Zhang H, Doree C, Mathur A, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. Sep 30 2015;(9):CD006536. doi:10.1002/14651858.CD006536.pub4

12. Gyongyosi M, Wojakowski W, Lemarchand P, et al. Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) in patients with acute myocardial infarction based on individual patient data. *Circ Res*. Apr 10 2015;116(8):1346-60. doi:10.1161/CIRCRESAHA.116.304346

13. 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. doi:10.1093/eurheartj/ehq449

14. 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 7 2014;115(11):950-60. doi:10.1161/CIRCRESAHA.115.303463

15. 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. doi:10.1161/CIRCRESAHA.115.308056

16. Lalu MM, Mazzarello S, Zlepnig 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. doi:10.1002/sctm.18-0120

17. Lee MS, Makkar RR. Stem-cell transplantation in myocardial infarction: a status report. *Ann Intern Med*. May 4 2004;140(9):729-37. doi:10.7326/0003-4819-140-9-200405040-00013

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

Resources: (cont.)

18. 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 6 2011;124(23):e574-651. doi:10.1161/CIR.0b013e31823ba622

19. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res*. Aug 5 2011;109(4):428-36. doi:10.1161/CIRCRESAHA.111.245993

20. 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. doi:10.1161/CIRCULATIONAHA.106.687376

21. Moazzami K, Roohi A, Moazzami B. Granulocyte colony stimulating factor therapy for acute myocardial infarction. *Cochrane Database Syst Rev*. May 31 2013;(5):CD008844. doi:10.1002/14651858.CD008844.pub2

22. 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. doi:10.1016/j.jacc.2012.11.019

23. 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. doi:10.1016/S0140-6736(16)30137-4

24. 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. doi:10.1007/s12265-009-9123-8

25. 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 8 2016;9(15):1576-85. doi:10.1016/j.jcin.2016.05.003

26. Schachinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med*. Sep 21 2006;355(12):1210-21. doi:10.1056/NEJMoa060186

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

Resources: (cont.)

27. Schachinger V, Erbs S, Elsasser 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. doi:10.1093/eurheartj/ehl388

28. 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. doi:10.1093/eurjhf/hfq095

29. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation*. Feb 22 2022;145(8):e153-e639. doi:10.1161/CIR.0000000000001052

30. 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. doi:10.1093/eurheartj/ehm485

31. U.S. Food and Drug Administration. Regenerative Medicine Advanced Therapy Designation. Accessed March 23, 2022. https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

32. 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. doi:10.1001/jama.2009.685

33. Wang S, Cui J, Peng W, Lu M. Intracoronary autologous CD34+ stem cell therapy for intractable angina. *Cardiology*. 2010;117(2):140-7. doi:10.1159/000320217

34. Writing C, Maddox TM, Januzzi JL, Jr., 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. doi:10.1016/j.jacc.2020.11.022

35. Writing Committee M, Lawton JS, Tamis-Holland JE, 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. doi:10.1016/j.jacc.2021.09.006

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

Resources: (cont.)

36. Xiao C, Zhou S, Liu Y, Hu H. Efficacy and safety of bone marrow cell transplantation for chronic ischemic heart disease: a meta-analysis. *Med Sci Monit*. Oct 1 2014;20:1768-77. doi:10.12659/MSM.892047

37. Xu R, Ding S, Zhao Y, Pu J, He B. 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. doi:10.1016/j.cjca.2014.01.013

Coding:

CPT: 38205, 38206, 38230, 38232, 38240, 38241

History:	Date:	Activity:
Medical Policy Panel	08/16/22	Approved guideline (Effective 09/19/22)

Policy Revisions:

EVIDENCE-BASED CRITERIA
SECTION: MEDICINE

ORIGINAL EFFECTIVE DATE: 09/19/22
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PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh íłínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.

PROGENITOR CELL THERAPY FOR THE TREATMENT OF DAMAGED MYOCARDIUM DUE TO ISCHEMIA (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:

اگر شما، یا کسی که شما به او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799
تماس حاصل نمایید.]

Assyrian:

[illegible] Blue Cross Blue Shield of Arizona، [illegible]
[illegible] 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคณ หรอคนทคณกาลงชวยเหลอมคาถามเกยวกบ Blue Cross Blue Shield of Arizona คณมสทธทจะไดรบความชวยเหลอและขอมลในภาษา ของคณไดโดยไมมคาใชจาย พดคยกบลาม โทร 877-475-4799