



MASSACHUSETTS

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

## Medical Policy

# Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant

### Table of Contents

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

### Policy Number: 338

BCBSA Reference Number: 2.03.03A

NCD/LCD: N/A

### Related Policies

None

### 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

Donor lymphocyte infusion may be **MEDICALLY NECESSARY** following allogeneic-hematopoietic cell transplantation (HCT) that was originally considered medically necessary for the treatment of a hematologic malignancy that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse, or to convert a patient from mixed to full donor chimerism.

Donor lymphocyte infusion is **INVESTIGATIONAL** following allogeneic-hematopoietic cell transplantation (HCT) that was originally considered investigational for the treatment of a hematologic malignancy.

Donor lymphocyte infusion is **INVESTIGATIONAL** as a treatment of nonhematologic malignancies following a prior allogeneic HCT.

Genetic modification of donor lymphocytes is **INVESTIGATIONAL**.

### 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
<b>Commercial Managed Care (HMO and POS)</b>	Prior authorization is <b>not required</b> .
<b>Commercial PPO and Indemnity</b>	Prior authorization is <b>not required</b> .
<b>Medicare HMO Blue<sup>SM</sup></b>	Prior authorization is <b>not required</b> .
<b>Medicare PPO Blue<sup>SM</sup></b>	Prior authorization is <b>not required</b> .

## 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

CPT codes:	Code Description
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

### Description

Approximately 40% to 60% of patients who receive a donor lymphocyte infusion (DLI) develop graft-versus-host disease (GVHD), and the development of GVHD predicts a response to the DLI. Treatment-related mortality after DLI is 5% to 20%. There does not seem to be a correlation between the type of hematologic malignancy for which the DLI is given and the development of GVHD.<sup>1</sup> The risk of developing GVHD is related, in part, to DLI dose and therapy before DLI.

DLI may be used for various indications such as relapse after allogeneic hematopoietic cell transplantation (HCT), to prevent disease relapse in the setting of T cell–depleted grafts or nonmyeloablative conditioning regimens, or to convert mixed to full donor chimerism. Management of relapse, which occurs in approximately 40% of all hematologic malignancy patients, is the most common indication for DLI.<sup>2</sup>

The literature is heterogeneous when reporting methods of cell collection, indication (eg, planned after chemotherapy, in early relapse), cell dose infused, and cell subtype used.<sup>1</sup> In addition, many studies include multiple diseases with little information on disease-specific outcomes; however, DLI is used in nearly all hematologic malignancies for which allogeneic HCT is performed, including chronic myeloid leukemia, acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes, multiple myeloma, and Hodgkin and non-Hodgkin lymphoma.

### Summary

Donor lymphocyte infusion (DLI), also called donor leukocyte or buffy-coat infusion, is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a hematopoietic cell transplant (HCT) from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or graft-versus-tumor effect due to recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells.

For individuals who have had an allogeneic HCT who receive DLI, the evidence includes nonrandomized comparative studies and case series. Relevant outcomes are overall survival and change in disease status. In various hematologic malignancies and for various indications such as planned or preemptive DLI, treatment of relapse, or conversion of mixed to full donor chimerism, patients have shown evidence of responding to DLI. Response rates to DLI for relapsed hematologic malignancies following an allogeneic HCT are best in chronic myelogenous leukemia (CML), followed by the lymphomas, multiple

myeloma, and acute leukemias, respectively. Other than CML, clinical responses are most effective when chemotherapy induction is used to reduce the tumor burden before DLI. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have had an allogeneic HCT who receive a modified (genetic or other ex vivo modification) donor lymphocytes infusion, the evidence includes case series. Relevant outcomes are overall survival and change in disease status. The case series have demonstrated the feasibility of the technique and no serious adverse effects. Without a comparison to standard treatment, the efficacy of administering modified donor lymphocytes is unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Policy History

Date	Action
4/2019	Prior authorization information clarified.
11/2016	BCBSA National medical policy review. Hematopoietic stem cell transplantation was replaced with hematopoietic cell transplantation in the policy statements, title, and text.
3/2016	New references added from BCBSA National medical policy.
7/2015	New references added from BCBSA National medical policy.
2/2014	Clarified coding information.
6/2013	New references from BCBSA National medical policy.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
1/1/2012	New medical policy describing medically necessary and investigational indications. Effective 1/1/2012.

## 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. Deol A, Lum LG. Role of donor lymphocyte infusions in relapsed hematological malignancies after stem cell transplantation revisited. *Cancer Treat Rev.* Nov 2010;36(7):528-538. PMID 20381970
2. Tomblyn M, Lazarus HM. Donor lymphocyte infusions: the long and winding road: how should it be traveled? *Bone Marrow Transplant.* Nov 2008;42(9):569-579. PMID 18711351
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). *Technology Assessment 1997*; Tab 22.
4. van den Brink MR, Porter DL, Giral S, et al. Relapse after allogeneic hematopoietic cell therapy. *Biol Blood Marrow Transplant.* Jan 2010;16(1 Suppl):S138-145. PMID 19857588
5. Simula MP, Marktel S, Fozza C, et al. Response to donor lymphocyte infusions for chronic myeloid leukemia is dose-dependent: the importance of escalating the cell dose to maximize therapeutic efficacy. *Leukemia.* May 2007;21(5):943-948. PMID 17361226
6. Dazzi F, Szydlo RM, Cross NC, et al. Durability of responses following donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. *Blood.* Oct 15 2000;96(8):2712-2716. PMID 11023502
7. Guglielmi C, Arcese W, Dazzi F, et al. Donor lymphocyte infusion for relapsed chronic myelogenous leukemia: prognostic relevance of the initial cell dose. *Blood.* Jul 15 2002;100(2):397-405. PMID 12091328

8. Fozza C, Szydlo RM, Abdel-Rehim MM, et al. Factors for graft-versus-host disease after donor lymphocyte infusions with an escalating dose regimen: lack of association with cell dose. *Br J Haematol.* Mar 2007;136(6):833-836. PMID 17341269
9. Radujkovic A, Guglielmi C, Bergantini S, et al. Donor lymphocyte infusions for chronic myeloid leukemia relapsing after allogeneic stem cell transplantation: may we predict graft-versus-leukemia without graft-versus-host disease? *Biol Blood Marrow Transplant.* Mar 19 2015. PMID 25797175
10. El-Jurdi N, Reljic T, Kumar A, et al. Efficacy of adoptive immunotherapy with donor lymphocyte infusion in relapsed lymphoid malignancies. *Immunotherapy.* May 2013;5(5):457-466. PMID 23638742
11. Guieze R, Damaj G, Pereira B, et al. Management of myelodysplastic syndrome relapsing after allogeneic hematopoietic stem cell transplantation: a study by the French Society of Bone Marrow Transplantation and Cell Therapies. *Biol Blood Marrow Transplant.* Aug 6 2015. PMID 26256942
12. Schmid C, Labopin M, Nagler A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol.* Nov 1 2007;25(31):4938-4945. PMID 17909197
13. Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a Center for International Blood and Marrow Transplant Research study. *Biol Blood Marrow Transplant.* Mar 2015;21(3):454-459. PMID 25460355
14. Warlick ED, DeFor T, Blazar BR, et al. Successful remission rates and survival after lymphodepleting chemotherapy and donor lymphocyte infusion for relapsed hematologic malignancies postallogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* Mar 2012;18(3):480-486. PMID 22155141
15. Schroeder T, Rachlis E, Bug G, et al. Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions-a retrospective multicenter analysis from the German Cooperative Transplant Study Group. *Biol Blood Marrow Transplant.* Apr 2015;21(4):653-660. PMID 25540937
16. Morris E, Thomson K, Craddock C, et al. Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. *Blood.* Dec 15 2004;104(13):3865-3871. PMID 15304395
17. Peggs KS, Sureda A, Qian W, et al. Reduced-intensity conditioning for allogeneic haematopoietic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: impact of alemtuzumab and donor lymphocyte infusions on long-term outcomes. *Br J Haematol.* Oct 2007;139(1):70-80. PMID 17854309
18. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor leukocyte infusions are effective in relapsed multiple myeloma after allogeneic bone marrow transplantation. *Blood.* Nov 15 1997;90(10):4206-4211. PMID 9354693
19. Salama M, Nevill T, Marcellus D, et al. Donor leukocyte infusions for multiple myeloma. *Bone Marrow Transplant.* Dec 2000;26(11):1179-1184. PMID 11149728
20. Collins RH, Jr., Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol.* Feb 1997;15(2):433-444. PMID 9053463
21. Bensinger WI, Buckner CD, Anasetti C, et al. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood.* Oct 1 1996;88(7):2787-2793. PMID 8839877
22. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor lymphocyte infusions for relapsed multiple myeloma after allogeneic stem-cell transplantation: predictive factors for response and long-term outcome. *J Clin Oncol.* Aug 2000;18(16):3031-3037. PMID 10944138
23. Ciceri F, Bonini C, Marktel S, et al. Antitumor effects of HSV-TK-engineered donor lymphocytes after allogeneic stem-cell transplantation. *Blood.* Jun 1 2007;109(11):4698-4707. PMID 17327416
24. Fowler DH, Mossoba ME, Steinberg SM, et al. Phase 2 clinical trial of rapamycin-resistant donor CD4+ Th2/Th1 (T-Rapa) cells after low-intensity allogeneic hematopoietic cell transplantation. *Blood.* Apr 11 2013;121(15):2864-2874. PMID 23426943
25. Hashimoto H, Kitano S, Ueda R, et al. Infusion of donor lymphocytes expressing the herpes simplex virus thymidine kinase suicide gene for recurrent hematologic malignancies after

- allogeneic hematopoietic stem cell transplantation. *Int J Hematol.* Jul 2015;102(1):101-110. PMID 25948083
26. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. v.1.2015. 2015; [http://www.nccn.org/professionals/physician\\_gls/pdf/cml.pdf](http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf). Accessed March, 2015.
  27. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia (v.2.2014). 2014; [http://www.nccn.org/professionals/physician\\_gls/pdf/all.pdf](http://www.nccn.org/professionals/physician_gls/pdf/all.pdf). Accessed March, 2015.
  28. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 4.2015. [http://www.nccn.org/professionals/physician\\_gls/pdf/myeloma.pdf](http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf). Accessed March, 2015.