

## Clinical Policy: Donor Lymphocyte Infusion

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### Description

This policy describes the medical necessity requirements for a donor lymphocyte infusion (DLI). DLI is an immune therapy approach to decrease the risk of relapse for many hematological malignancies following allogeneic hematopoietic stem cell transplantation (HSCT), or to convert a patient's mixed to full donor chimerism, a state where both donor and recipient stem cells coexist. In this procedure, donor lymphocytes from the original stem cell donor are infused into the patient to cause an immune-mediated graft vs. tumor response. The hematological malignancies treated by DLIs can include, but not limited to, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lymphomas, multiple myeloma, and myelodysplastic syndrome.

### Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation® that donor lymphocyte infusion is **medically necessary** following an allogeneic hematopoietic stem cell transplantation (HSCT) for any of the following indications:
  - A. To decrease the risk of relapse of hematological malignancy;
  - B. To convert the recipient stem cells of the donor from mixed to full donor chimerism if there is a concern for relapse. DLI should not be used for the sole purpose of increasing donor chimerism without the risk of relapse.
- II. It is the policy of health plans affiliated with Centene Corporation that donor lymphocyte infusion is considered **experimental/investigational** for any of the following:
  - A. For the treatment of all other conditions than those specified above;
  - B. Genetic modification or *ex vivo* manipulation of donor lymphocytes;
  - C. In the presence of higher than grade 2 acute graft-versus-host-disease (GvHD);
  - D. In the presence of total host chimerism.

### Background

In addition to chemotherapy, HSCT has become a mainstream clinical therapy for a variety of hematological malignancies. Even though the anti-tumor effects of HSCT can be durable for some patients, relapse of the original malignancy presents considerable clinical challenges for 40 to 75% of patients who undergo autologous HSCT and 10 to 40% of those who undergo allogeneic HSCT.<sup>1</sup> Therefore, salvage therapies to combat the refractory disease are required. DLI is one such post-transplant immunotherapy.

Donor lymphocyte infusion, otherwise known as buffy coat infusion, was originally described in 1990 by Kolb and colleagues as a treatment protocol for three patients who had relapsed after bone marrow transplantation for CML.<sup>2</sup> In this procedure, mononuclear cells collected by apheresis from the related or unrelated donor who provided the original hematopoietic stem cell graft are infused into the patient to harness the graft vs. tumor effect. While there is some variety

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in published reports concerning the dose of donor cells infused, Deol and Lum survey several articles and report an effective cellular range of  $0.01$  to  $8.8 \times 10^8$  T cells/kg.<sup>3</sup>

The precise mechanism of action, including the tumor-specific antigens as well as the critical effector cells that mediate the anti-tumor immune response, has not yet been fully elucidated. However, recent evidence suggests that both donor T cells and host-derived immune compartments, including antigen presenting cells and B cells, among others, are critical for facilitating the graft vs. tumor effect of DLI.<sup>1,3,4</sup>

In striving to eradicate the tumor cell population from the host, complications may persist in patients treated with DLI. Graft vs. host disease (GvHD), the most common and significant toxicity attributable to DLI, occurs in approximately in 40-60% of patients, according to a range of several published reports.<sup>1,4,5</sup> GvHD ensues when the transplanted donor cells recognize the host as foreign and initiate an immune reaction that usually affects the patient's skin, gastrointestinal tract, and/or liver.<sup>6</sup> However, there is a strong correlation observed with the onset of GvHD and the intended graft vs. tumor effect. The onset of GvHD is independent of the type of hematological malignancy. In a retrospective study, Collins et al. observed that of 140 patients treated with DLI for relapsed disease after stem cell transplant, approximately 60% patients present with GvHD; of these, 42/45 patients in complete response of disease developed acute GvHD and 36/41 patients in complete response of disease displayed chronic GvHD.<sup>7</sup> Nevertheless, Carlens et al. determined that the 3 year leukemia free survival is greater for patients who develop chronic GvHD than for those who do not.<sup>8</sup> Therefore, the ultimate goal of DLI is to maximize the graft vs. tumor response while minimizing the complications that arise from the related GvHD.

In addition to GvHD, bone marrow aplasia is another major complication that can occur in 2-5% of patients following DLI.<sup>9</sup> Infection and bleeding are compounding risks associated with the onset of aplasia following DLI. The infusion of subsequent donor stem cells can reverse marrow aplasia.

Since Kolb's initial study describing the utility of DLI, focus has been placed on evaluating the clinical benefit of DLI in the context of treating relapsed CML. Multiple studies have revealed that DLI can establish complete remissions in 70-80% of patients with relapsed CML, and the response is durable in the majority of these cases.<sup>9</sup>

DLI is less effective for achieving remission in patients with relapsing AML following HSCT. According to Deol and Lum, the ability of DLI to induce remission in relapsed AML is approximately 15-20%.<sup>3</sup> However, unlike the observations made for CML, it is often necessary to combine DLI with a chemotherapy regimen to elicit an anti-tumor effect against AML.

Multiple myeloma is another hematological malignancy with the potential to respond to DLI. Among varying reports, the response rate of relapsed multiple myeloma to DLI is approximately 22-52%.<sup>10,11</sup> The propensity of multiple myeloma patients to receive autologous and not allogeneic transplants could have a role in this outcome.<sup>3</sup> NCCN guidelines state that in patients whose disease does not respond to or relapses after allogeneic stem cell grafting may receive

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DLI to stimulate a beneficial graft-versus-myeloma effect or other myeloma therapies on or off a clinical trial.<sup>18</sup>

Furthermore, DLI is a treatment possibility for relapsed ALL. However the outcomes for relapsed ALL have been less robust compared to CML and AML. Collins et al analyzed outcomes in both retrospective and prospective studies in patients with relapsed ALL treated with chemotherapy and DLI, and found that only 3/44 were disease free.<sup>7</sup>

Lastly, chimerism is an important element that develops after the engraftment of a HSCT. Mixed chimerism is defined when < 90% donor cells are detected, whereas full or complete chimerism is defined as 100% donor cells detected, suggesting completed hematopoietic replacement.<sup>12</sup> One such example of the graft vs. tumor effects observed from the conversion to full chimerism was described by Orisini, in which 4 patients with relapsed multiple myeloma received DLI specifically with CD4<sup>+</sup> T cells. It was observed that 3/4 patients saw a clinical response in the absence of GvHD with complete hematopoietic conversion.<sup>13</sup>

In summary, donor lymphocyte infusion is an effective clinical treatment for an array of relapsed hematological malignancies. For this adoptive immunotherapy, T lymphocytes from the original stem cell donor are infused into the patient with the intent of inducing a graft vs. tumor response.

**Coding Implications**

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CPT®* Codes	Description
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38242	Allogeneic lymphocyte infusions
86950	Leukocyte transfusion

HCPCS Codes	Description
S2150	Bone marrow or blood-derived stem-cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

**ICD-10-CM Diagnosis Codes that Support Coverage Criteria**

ICD-10-CM Code	Description
C81.00 - C81.99	Hodgkin lymphoma
C85.10 - C85.99	Other specified and unspecified types of non-Hodgkin lymphoma
C90.00 - C90.02	Multiple myeloma
C91.00 - C91.Z2	Lymphoid leukemia
C92.00 - C92.Z2	Myeloid leukemia
D46.0 - D46.Z	Myelodysplastic syndrome
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed	11/15	11/15
Clarified in I. that DLI is indicated post <i>allogenic</i> HSCT; also added post bone marrow transplant. Added II C: Repeat DLI not medically necessary if no documented positive response from the first. Made minor wording changes in the background. Added CPT codes 38215 and 86950. Added HCPCS and ICD-10 codes.	10/16	11/16
References reviewed and updated. Code updates.	10/17	11/17
Removed “who has not relapsed” from I.B. Background updated. References reviewed and updated.	10/18	10/18
References reviewed and updated. Specialist review.	09/19	10/19
Description updated. Specified in I.A. that DLI is indicated to reduce the risk of relapse. Added to I.B. that DLI is intended to convert recipient cells from mixed to full chimerism, if there is a risk of relapse. Added to II. “higher than grade 2 acute graft-versus-host-disease (GvHD)” and “total host chimerism.” Removed not medically necessary indication from section II. of a second DLI when benefits were not noted from the first. References reviewed and updated. Specialist review. Replaced “member” with “member/enrollee” in all instances.	10/20	10/20

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### **Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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**Note: For Medicare members/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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