Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052
Original Effective Date: 01/28/2002
Current Effective Date: 10/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas is addressed separately in medical policy 00062.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma in patients with markers of poor-risk disease to be **eligible for coverage.**** (see Policy Guidelines and Rationale). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) except as noted above to be **investigational.***

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Based on review of available data, the Company considers autologous hematopoietic cell transplantation (HCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) to be **investigational.***

Policy Guidelines

Staging and Prognosis of Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Two scoring systems are used to determine stage and prognosis of patients with CLL or SLL. As outlined in Table PG1, the Rai and Binet staging systems classify patients into 3 risk groups with different prognoses and are used to make therapeutic decisions.

Table PG1. Rai and Binet Classification for CLL or SLL

Rai Stage	Risk	Description	Median Survival, y	Binet Stage	Description	Median Survival, y
0	Low	Lymphocytosis	>10	A	≤3 lymphoid areas, normal hemoglobin and platelets	>10
I	Int	Lymphocytosis + lymphadenopathy	7-9	B	≥3 lymphoid areas, normal hemoglobin and platelets	7
II	Int	Lymphocytosis + splenomegaly ± lymphadenopathy	7-9			
III	High	Lymphocytosis + anemia ± lymphadenopathy or splenomegaly	1.5-5	C	Any number of lymphoid areas, anemia, thrombocytopenia	5
IV	High	Lymphocytosis + thrombocytopenia ±	1.5-5			

		anemia, splenomegaly, or lymphadenopathy				

CLL: chronic lymphocytic leukemia; Int: Intermediate; SLL: small lymphocytic lymphoma.

Because prognoses of patients vary within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. They are summarized in Table PG2, according to availability in clinical centers.

Table PG2. Markers of Poor Prognosis in CLL or SLL

Community Center	Specialized Center
•Advanced Rai or Binet stage	•IgVh wild type
•Male sex	•Expression of ZAP-70 protein
•Atypical morphology or CLL or SLL	•Del(11q22-q23) (loss of *ATM* genet)
•Peripheral lymphocyte doubling time <12 mo	•del(17p13)/variant *TP53*
•CD38-positive	•Trisomy 12
•Elevated β_2-microglobulin level	•Elevated serum CD23
•Diffuse marrow histology	•Elevated serum tumor necrosis factor-α
•Elevated serum lactate dehydrogenase level	•Elevated serum thymidine kinase
•Fludarabine resistance	

IgVh: immunoglobulin heavy-chain variable-region

An expert panel convened by the American Society for Blood and Marrow Transplantation was queried about criteria used to define high-risk CLL, as part of the process for developing 2016 guidelines. Panelists responded that criteria are presence of 17p deletion (del17p)

and/or*TP53* variants (100%) and presence of complex karyotype (67%). The National Comprehensive Cancer Network guideline on CLL/SLL stated the following as unfavorable prognostic factors: DNA sequencing with mutated *TP53* or ≤2% immunoglobulin heavy-chain variable (*IGHV)* mutation; interphase cytogenetics with del17p or deletion of 11q (del11q); or complex karyotype (≥3 unrelated chromosome abnormalities in more than 1 cell on karyotype).

Reduced-Intensity Conditioning for Allogeneic Hematopoietic Cell Transplantation
Some patients for whom a conventional myeloablative allotransplant could be curative may be considered as candidates for reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (allo-HCT). These include those patients whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allo-HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC before a second allo-HCT if complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are human leukocyte antigen (HLA)- identical siblings, matched at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Related donors mismatched at a single locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, haploidentical donors-typically a parent or a child of the patient-with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens, have been under investigation as a stem cell source. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Background/Overview

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
CLL and SLL are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in the blood, bone marrow, lymph nodes, and spleen; in SLL they are generally confined

to lymph nodes. The Revised European-American/World Health Organization Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

Chronic lymphocytic leukemia and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent, but can undergo transformation to a more aggressive form of the disease (eg, Richter transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as a poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and treatment outcomes are comparable for both diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses, with median survivals of 6 to 10 years; however, the median survival of high-risk CLL or SLL may only be 2 years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural disease history prompted an investigation of HCT as a possible curative regimen.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor allo-HCT. These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of HLA using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning for Hematopoietic Cell Transplantation

The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. The slower graft-versus-malignancy effect is considered the potentially curative component, but it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse events that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases the susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. Reduced-intensity conditioning regimens can be viewed as a continuum in effects, from near totally

myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow-mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

Rationale/Source

Risk stratification of patients with CLL/SLL guides therapy decisions, which may include HCT for those with poor risk features.

Summary of Evidence

For individuals who have CLL/SLL and markers of poor-risk disease who receive allogeneic HCT (allo-HCT), the evidence includes single-arm prospective and registry-based studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data have suggested that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. High rates of treatment-related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CLL/SLL who receive autologous HCT, the evidence includes randomized controlled trials and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies

of autologous HCT published to date have not shown improvement in overall survival in patients with CLL/SLL, and results must be considered in the context of improved outcomes with the use of newer chemoimmunotherapy agents. Furthermore, evidence from the European Intergroup randomized controlled trial has suggested the quality of life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Clinical input was sought to help determine whether the use of HCT for individuals with CLL would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, input was received from 1 specialty medical center reviewer, 1 academic medical center reviewer, and 2 Blue Distinction Center reviewers while this policy was under review in 2010. Three of 4 reviewers agreed that allo-HCT was of value to patients with poor risk CLL (see Policy Guidelines section) and that this procedure should be medically necessary for this setting. However, reviewers indicated that the specific approach (eg, reduced-intensity conditioning versus myeloablative conditioning) should be individualized based on criteria such as age and health status. For individuals who have CLL who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice. All reviewers concurred with the policy statement that autologous HCT is investigational.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

Clinical input was sought to help determine whether the use of hematopoietic cell transplantation for individuals with CLL would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, input

was received from 1 specialty medical center reviewer, 1 academic medical center reviewer, and 2 Blue Distinction Center reviewers while this policy was under review in 2010. Three of 4 reviewers agreed that allo-HCT was of value to patients with poor-risk CLL (see Policy Guidelines section) and that this procedure should be medically necessary for this setting. However, reviewers indicated that the specific approach (eg, reduced-intensity conditioning vs myeloablative conditioning) should be individualized based on criteria such as age and health status. For individuals who have CLL who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice. All reviewers concurred with the policy statement that autologous HCT is investigational.

Practice Guidelines and Position Statements
American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation published guidelines on indications for allo-HCT and autologous HCT for CLL. Recommendations described the current consensus on the use of HCT in and out of the clinical trial setting. Treatment recommendations are shown in Table 1.

Table 1. 2015 Recommendations for Allogeneic and Autologous Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia

Adult Indications	Allogeneic HCT	Autologous HCT
High-risk, first or greater remission	C	N
T cell, prolymphocytic leukemia	R	R
B cell, prolymphocytic leukemia	R	R
Transformation to high-grade lymphoma	C	C

C: standard of care, clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication.

In 2016, the Society published clinical practice recommendations with additional detail on allo-HCT for CLL. Recommendations are shown in Table 2.

Table 2. 2016 Recommendations for Allogeneic Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia

Indications	Allogeneic HCT
High-risk CLL	Not recommended in the first-line consolidation setting
	Not recommended for patients who relapse after first-line therapy and demonstrate sensitive disease after second-line therapy (not BCR inhibitors)
	Recommended for patients who relapse after first-line therapy, have refractory disease after second-line therapy (not BCR inhibitors), and show an objective response to BCR inhibitors or to a clinical trial
	Recommended for patients who relapse after first-line therapy, have refractory disease after second-line therapy (including BCR inhibitors but not BCL-2 inhibitors), and show an objective response to BCL-2 inhibitors or to a clinical trial
	Recommended when there is a lack of response or there is progression after BCL-2 inhibitors
Richter transformation	Recommended after achieving an objective response to anthracycline-based chemotherapy
Purine analogue relapsed and/or refractory disease	Not recommended

BCR: B-cell receptor; BCL-2: B-cell lymphoma 2; CLL: chronic lymphocytic leukemia; HCT: hematopoietic cell transplantation.

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network guidelines (v.1.2021) for CLL and small lymphocytic lymphoma (SLL) state the following regarding HCT:

- "Allogeneic HCT can be considered for CLL/SLL refractory to small-molecule therapy in patients without significant comorbidities."
- "For patients with CLL/SLL with del(17p) or *TP53* mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if complex karyotype [CK] (≥3 abnormalities) is present. However, available data suggest that CK (≥5 abnormalities) is associated with inferior overall survival [OS] and event-free survival [EFS] following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics."
- In patients with histologic transformation (Richter's) and progression, allogeneic HCT can be considered for certain patients with disease responding to initial chemotherapy. In addition, "autologous HCT may also be appropriate for patients with disease responding to initial therapy but who are not candidates for allogeneic HCT due to age, comorbidities, or lack of a suitable donor."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma", 8.01.15 February 2021.
2. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

3. Gine E, Moreno C, Esteve J, et al. The role of stem-cell transplantation in chronic lymphocytic leukemia risk-adapted therapy. Best Pract Res Clin Haematol. Sep 2007; 20(3): 529-43. PMID 17707838
4. Gribben JG. Role of allogeneic hematopoietic stem-cell transplantation in chronic lymphocytic leukemia. J Clin Oncol. Oct 20 2008; 26(30): 4864-5. PMID 18794537
5. Kharfan-Dabaja MA, Anasetti C, Santos ES. Hematopoietic cell transplantation for chronic lymphocytic leukemia: an evolving concept. Biol Blood Marrow Transplant. Apr 2007; 13(4): 373-85. PMID 17382245
6. Gladstone DE, Fuchs E. Hematopoietic stem cell transplantation for chronic lymphocytic leukemia. Curr Opin Oncol. Mar 2012; 24(2): 176-81. PMID 22234253
7. Delgado J, Milligan DW, Dreger P. Allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia: ready for prime time?. Blood. Sep 24 2009; 114(13): 2581-8. PMID 19641189
8. Dreger P. Allotransplantation for chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2009: 602-9. PMID 20008245
9. Brown JR, Kim HT, Li S, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. Biol Blood Marrow Transplant. Oct 2006; 12(10): 1056-64. PMID 17084369
10. Delgado J, Thomson K, Russell N, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. Blood. Feb 15 2006; 107(4): 1724-30. PMID 16239425
11. Dreger P, Brand R, Hansz J, et al. Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. Leukemia. May 2003; 17(5): 841-8. PMID 12750695
12. Khouri IF, Saliba RM, Admirand J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. Br J Haematol. May 2007; 137(4): 355-63. PMID 17456058
13. Schetelig J, Thiede C, Bornhauser M, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. J Clin Oncol. Jul 15 2003; 21(14): 2747-53. PMID 12860954

14. Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol. Oct 20 2008; 26(30): 4912-20. PMID 18794548
15. Dreger P, Dohner H, Ritgen M, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood. Oct 07 2010; 116(14): 2438-47. PMID 20595516
16. Reljic T, Kumar A, Djulbegovic B, et al. High-dose therapy and autologous hematopoietic cell transplantation as front-line consolidation in chronic lymphocytic leukemia: a systematic review. Bone Marrow Transplant. Aug 2015; 50(8): 1144. PMID 26242579
17. Michallet M, Dreger P, Sutton L, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. Blood. Feb 03 2011; 117(5): 1516-21. PMID 21106985
18. de Wreede LC, Watson M, van Os M, et al. Improved relapse-free survival after autologous stem cell transplantation does not translate into better quality of life in chronic lymphocytic leukemia: lessons from the randomized European Society for Blood and Marrow Transplantation-Intergroup study. Am J Hematol. Feb 2014; 89(2): 174-80. PMID 24123244
19. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Nov 2015; 21(11): 1863-1869. PMID 26256941
20. Kharfan-Dabaja MA, Kumar A, Hamadani M, et al. Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Dec 2016; 22(12): 2117-2125. PMID 27660167

Policy History

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12/06/2001 Medical Policy Committee review
01/28/2002 Managed Care Advisory Council approval
06/24/2002 Format revision. Coverage eligibility policy unchanged.

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03/31/2004	Medical Director review
04/20/2004	Medical Policy Committee review. Format revision.
04/26/2004	Managed Care Advisory Council approval
06/03/2005	Medical Director review
06/21/2005	Medical Policy Committee review. Format revision. Rationale and Source added.
07/15/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/01/2007	Medical Director review
08/15/2007	Medical Policy Committee approval. Rationale/Source updated. Coverage eligibility unchanged.
08/06/2009	Medical Policy Committee approval.
08/26/2009	Medical Policy Implementation Committee approval. Rationale/Source updated. Coverage eligibility unchanged. Title changed.
07/01/2010	Medical Policy Committee approval.
07/21/2010	Medical Policy Implementation Committee approval. Policy statement regarding allogeneic transplant in patients with markers of poor-risk disease changed; now may be considered medically necessary.
07/07/2011	Medical Policy Committee approval.
07/20/2011	Medical Policy Implementation Committee approval. No change to coverage.
06/28/2012	Medical Policy Committee review
07/27/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding updated
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review

09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. The word stem was removed from title and body of the policy.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Added policy guidelines.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2022

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C91.10-C91.Z2

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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