Corporate Medical Policy

Hematopoietic Cell Transplantation

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Description of Procedure or Service

Hematopoietic Stem-Cell Transplantation Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They 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 "naïve" and thus are associated with a lower incidence of graft-versus-host disease (GVHD). (Refer to the policy "Cord Blood as a Source of Stem Cells). Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte antigens (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.

This policy addresses hematopoietic stem cell transplantation (HSCT) in the treatment of the following select leukemias, lymphoma, myelodysplastic disorders and other malignancies:

- Acute Myeloid Leukemia (AML)
- Acute Lymphoblastic Leukemia (ALL)
- Chronic Myeloid Leukemia (CML)
- Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
- Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- Hematopoietic Cell Transplantation for Non-Hodgkin Lymphoma
- Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Multiple Myeloma, Poems Syndrome
- Hematopoietic Cell Transplantation for Waldenstrom Macroglobulinemia
- Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- Hematopoietic Cell Transplantation for Solid Tumors Childhood
- Hematopoietic Cell Transplantation for Germ Cell Tumors
- Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- Allogeneic Hematopoietic Transplant for Genetic Diseases and Acquired Aplastic Anemia
- Hematopoietic Cell Transplantation for Autoimmune Diseases
- Hematopoietic Cell Transplantation for Primary Amyloidosis

Related Policies:
Cord Blood as a Source of Stem Cells

Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for hematopoietic cell transplantation when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

If the medical criteria and guidelines are not met, some patients may be eligible for coverage under clinical trials. Refer to the policy, Clinical Trial Services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.

When Hematopoietic Cell Transplantation is covered

I. Acute Myeloid Leukemia (AML)

A. Allogeneic hematopoietic stem-cell transplantation (HSCT) using a myeloablative conditioning regimen may be considered medically necessary to treat:
1. Poor- to intermediate-risk AML in first complete remission (CR1); **or**
2. AML that is refractory to standard induction chemotherapy but can be brought into CR with intensified induction chemotherapy; **or**
3. AML that relapses following chemotherapy induced CR1 but can be brought into CR2 or beyond with intensified induction chemotherapy; **or**
4. AML in patients who have relapsed following a prior autologous HCT, however, can be brought into CR with intensified induction chemotherapy and are medically able to tolerate the procedure.

B. Allogeneic HSCT using a reduced-intensity conditioning regimen may be considered medically necessary as a treatment of AML in patients who are in complete marrow and extramedullary remission (CR1 or beyond), and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen.

C. Autologous HSCT may be considered medically necessary to treat AML in CR1 or beyond, or relapsed AML if responsive to intensified induction chemotherapy.

II. Acute Lymphoblastic Leukemia (ALL)

Children

A. Allogeneic or autologous cell transplantation may be considered medically necessary as a treatment of childhood ALL in first complete remission but at high risk of relapse.

B. Autologous or allogeneic cell transplantation may be considered medically necessary as a treatment of childhood ALL in second or greater remission or refractory ALL.

C. Allogeneic HCT is considered medically necessary to treat relapsing ALL after a prior autologous HCT.

Adults

A. Autologous hematopoietic cell transplantation may be considered medically necessary as a treatment of adult ALL in first complete remission but at high risk of relapse.
B. Allogeneic hematopoietic cell transplantation may be considered medically necessary as a treatment of adult ALL in first complete remission for any risk level.
C. Allogeneic hematopoietic cell transplantation may be considered medically necessary as a treatment of adult ALL in second or greater remission, or in adults with relapsed or refractory ALL.
D. Reduced-intensity conditioning allogeneic hematopoietic HCT may be considered medically necessary as a treatment of ALL patients who are in complete marrow and extramedullary first or second remission, and who, for medical reasons would be unable to tolerate a standard myeloablative conditioning regimen.
E. High dose chemotherapy with allogeneic cell support may be considered medically necessary as a treatment in adults with Progenitor-B cell ALL.
F. Allogeneic HCT is considered medically necessary to treat relapsing ALL after a prior autologous HCT.

III. Chronic Myeloid Leukemia (CML)

A. Allogeneic cell transplantation using a myeloablative conditioning regimen may be considered medically necessary as a treatment of chronic myeloid leukemia.
B. Allogeneic hematopoietic cell transplantation using a reduced-intensity conditioning (RIC) regimen may be considered medically necessary as a treatment of chronic myeloid leukemia in patients who meet clinical criteria for an allogeneic HCT but who are not considered candidates for a myeloablative conditioning allogeneic HCT.

IV. Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

A. Allogeneic hematopoietic cell transplantation may be considered medically necessary to treat chronic lymphocytic leukemia or small lymphocytic lymphoma in patients with markers of poor-risk disease.
B. 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.

V. Hodgkin Lymphoma

A. Autologous hematopoietic cell transplantation (HCT) may be considered medically necessary in patients with primary refractory Hodgkin's disease or relapsed Hodgkin lymphoma (HL).
B. Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered medically necessary in patients with primary refractory or relapsed Hodgkin lymphoma.

VI. Non-Hodgkin Lymphoma

A. For patients with non-Hodgkin lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic stem cell transplantation (HSCT) using a myeloablative conditioning regimen or autologous HSCT may be considered medically necessary:
   1. as salvage therapy for patients who do not achieve a complete remission (CR) after first line treatment (induction) with a full course of standard-dose chemotherapy;
   2. to achieve or consolidate a CR for those in a chemo-sensitive first or subsequent relapse; or
   3. to consolidate a first CR in patients with diffuse large B-cell lymphoma, with an age adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse.
B. For patients with mantle cell lymphoma:
   1. autologous HSCT may be considered medically necessary to consolidate a first remission.

2. allogeneic HSCT, myeloablative or reduced-intensity conditioning, may be considered medically necessary as salvage therapy.

C. For patients with NHL B-cell subtypes considered indolent, either allogeneic HSCT using a myeloablative conditioning regimen or autologous HSCT may be considered medically necessary:
1. as salvage therapy for patients who do not achieve CR after first-line treatment (induction) with a full course of standard-dose chemotherapy; **or**
2. to achieve or consolidate CR for those in a first or subsequent chemo-sensitive relapse, whether or not lymphoma has undergone transformation to a higher grade.

D. Reduced-intensity conditioning allogeneic HSCT may be considered medically necessary as a treatment of NHL in patients who meet criteria for an allogeneic HSCT but who do not qualify for a myeloablative allogeneic HSCT.

E. For patients with mature T-cell or NK-cell (peripheral T-cell) neoplasms:
1. autologous HSCT may be considered medically necessary to consolidate a first complete remission in high-risk subtypes.
2. autologous or allogeneic HSCT (myeloablative or reduced-intensity conditioning) may be considered medically necessary as salvage therapy.

VII. Plasma Cell Dyscrasias, Multiple Myeloma, POEMS Syndrome

A. Multiple Myeloma
1. A single or second (salvage) autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma.
2. Tandem autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma in patients who fail to achieve at least a near-complete or very good partial response after the first transplant in tandem sequence.
3. Tandem transplantation with an initial round of autologous hematopoietic cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic cell transplantation (i.e., reduced-intensity conditioning transplant) may be considered medically necessary to treat newly diagnosed multiple myeloma patients.

B. POEMS Syndrome
1. Autologous hematopoietic cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome.

VIII. Waldenstrom Macroglobulinemia

A. Autologous hematopoietic stem-cell transplantation may be considered medically necessary as salvage therapy of chemosensitive Waldenstrom macroglobulinemia.

IX. Miscellaneous Solid Tumors in Adults

A. Hematopoietic stem-cell transplantation may be covered for members participating in a clinical trial.

X. Solid Tumors Childhood

A. Autologous hematopoietic stem-cell transplantation may be considered medically necessary for:
1. initial treatment of high-risk neuroblastoma,
2. recurrent or refractory neuroblastoma,
3. initial treatment of high-risk Ewing's sarcoma,
4. recurrent or refractory Ewing's sarcoma, **and**
5. metastatic retinoblastoma.

B. Tandem autologous hematopoietic stem-cell transplantation may be considered medically necessary for high-risk neuroblastoma.

XI. Germ Cell Tumors

A. Single autologous hematopoietic stem-cell transplantation may be considered medically necessary as salvage therapy for germ-cell tumors:
   1. in patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; **or**
   2. in patients with unfavorable prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease.

B. Tandem or sequential autologous hematopoietic stem-cell transplantation may be considered medically necessary for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

XII. CNS Embryonal Tumors and Ependymoma

A. Embryonal tumors of the CNS: Autologous hematopoietic stem-cell transplantation may be considered medically necessary as consolidation therapy for previously untreated embryonal tumors of the central nervous system (CNS) that show partial or complete response to induction chemotherapy, or stable disease after induction therapy.

B. Autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat recurrent embryonal tumors of the CNS.

XIII. Allogeneic HCT for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

A. Allogeneic hematopoietic cell transplantation (HCT) may be considered medically necessary as a treatment of:
   1. myelodysplastic syndromes, **or**
   2. myeloproliferative neoplasms

B. Reduced-intensity conditioning allogeneic HCT may be considered medically necessary in patients who are at high-risk of intolerance for risk-adapted treatment of:
   1. myelodysplastic syndromes, **or**
   2. myeloproliferative neoplasms

XIV. Allogeneic HCT for Genetic Diseases and Acquired Anemia

A. Allogeneic hematopoietic transplant for genetic diseases and acquired anemias are considered medically necessary for selected patients with the following disorders:
   1. Hemoglobinopathies
      • Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage
      • Homozygous beta-thalassemia (i.e., thalassemia major)
   2. Bone marrow failure syndromes
      •Aplastic anemia including hereditary (e.g., Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond, Diamond-Blackfan) or acquired (e.g., secondary to drug or toxin exposure) forms
   3. Primary immunodeficiencies
      • Absent or defective T-cell function (e.g., severe combined immunodeficiency, WiskottAldrich syndrome, X-linked lymphoproliferative syndrome)
      • Absent or defective natural killer function (e.g. Chediak-Higashi syndrome)
      • Absent or defective neutrophil function (e.g. Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect)
   4. Inherited metabolic disease
      • Lysosomal and peroxisomal storage disorders except Hunter, Sanfilippo, and Morquio syndromes
   5. Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease).

XV. Autoimmune Diseases

A. Autologous hematopoietic cell transplantation is considered medically necessary as a treatment of systemic sclerosis/scleroderma if **ALL** of the following conditions are met:
   1. adult patients <69 years of age; **AND**
   2. maximum duration of scleroderma of 5 years: **AND**
   3. modified Rodnan Scale Scores >15; **AND**
   4. internal organ involvement; **AND**
   5. history of < 6 months treatment with cyclophosphamide; **AND**
   6. no active gastric antral vascular ectasia

XVI. Primary Amyloidosis

A. Autologous hematopoietic stem-cell transplantation may be considered medically necessary to treat primary systemic amyloidosis.

When Hematopoietic Cell Transplantation is not covered

The following is considered investigational for [all applications}. BCBSNC does not provide coverage for investigational services or procedures:

1. **ALL**: Autologous HCT is investigational to treat adult ALL in second or greater remission or those with refractory disease.
2. **CML**: Autologous HCT is considered investigational as a treatment of (CML) chronic myeloid leukemia.
3. **CML/SLL**: Autologous hematopoietic cell transplantation is considered investigational to treat CML or SLL.
4. **Hodgkin Lymphoma**: A second autologous cell transplantation (HCT) for relapsed lymphoma after a prior autologous HCT is considered investigational for Hodgkin lymphoma.
   Tandem autologous HCT is considered investigational.
   Other uses of HCT in patients with Hodgkin lymphoma are considered investigational, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission.
5. **Non-Hodgkin Lymphoma**: For patients with mantle cell lymphoma, autologous HSCT is considered investigational as salvage therapy and allogeneic HSCT is considered investigational to consolidate a first remission.
   Either autologous HSCT or allogeneic HSCT is considered investigational as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL; or to consolidate a first complete remission (CR) for patients with diffuse large B-cell lymphoma and an International Prognostic Index score that predicts a low- or low-intermediate risk of relapse; or to consolidate a first complete remission (CR) for those with indolent NHL B-cell subtypes.
   Tandem transplants are considered investigational to treat patients with any stage, grade, or subtype of NHL.
   For patients with mature T-cell or NK-cell (peripheral T-cell) neoplasms, allogeneic HSCT is considered investigational to consolidate a first remission.
6. **Plasma Cell Dyscrasias, Multiple Myeloma, POEMS Syndrome**: Allogeneic hematopoietic cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered investigational.
   Allogeneic and tandem hematopoietic cell transplantation are considered investigational to treat POEMS syndrome.
7. **Waldenstrom Macroglobulinemia**: Allogeneic hematopoietic stem-cell transplantation is considered investigational to treat Waldenstrom macroglobulinemia.
8. **Epithelial Ovarian Cancer**: Autologous or allogeneic hematopoietic stem-cell transplantation is considered investigational as a treatment of epithelial ovarian cancer.

9. **Miscellaneous Solid Tumors in Adults**: Autologous or allogeneic hematopoietic stem-cell transplantation is considered investigational for miscellaneous solid tumors including, but not limited to the following, unless they are part of a clinical trial **(see Clinical Trial Services policy):** • Lung cancer, any histology; • Colon cancer; • Rectal cancer; • Pancreas cancer; • Stomach cancer; • Esophageal cancer; • Gall bladder cancer; • Cancer of the bile duct; • Renal cell cancer; • Cervical cancer; • Uterine cancer; • Cancer of the fallopian tubes; • Prostate cancer; • Nasopharyngeal cancer; • Paranasal sinus cancer; • Neuroendocrine tumors; • Soft tissue sarcomas; Thyroid tumors; • Tumors of the thymus; • Tumors of unknown primary origin; • Malignant melanoma; • Undifferentiated tumors.
10. **Solid Tumors of Childhood**: Autologous hematopoietic stem-cell transplantation is considered investigational as initial treatment of low- or intermediate-risk neuroblastoma, initial treatment of low- or intermediate risk Ewing's sarcoma, and for other solid tumors of childhood including, but not limited, to the following: • rhabdomyosarcoma • Wilms tumor • osteosarcoma • retinoblastoma without metastasis.
    Tandem autologous hematopoietic stem-cell transplantation is considered investigational for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma, as noted above.
    Salvage allogeneic hematopoietic stem-cell transplantation pediatric solid tumors that relapse after autologous transplant or fail to respond is considered investigational.
    Allogeneic (myeloablative or nonmyeloablative) hematopoietic stem-cell transplantation is considered investigational for treatment of pediatric solid tumors.
11. **Germ Cell Tumors**: Autologous hematopoietic stem-cell transplantation is considered investigational as a component of first-line treatment for germ-cell tumors.
    Allogeneic hematopoietic stem-cell transplantation is considered investigational to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous hematopoietic stem-cell transplantation.
12. **Embryonal tumors of the CNS**: Allogeneic hematopoietic stem-cell transplantation is investigational to treat embryonal tumors of the CNS.
    Tandem autologous hematopoietic stem-cell transplant is investigational to treat embryonal tumors of the CNS.
    Ependymoma: Autologous, tandem autologous and allogeneic hematopoietic stem-cell transplant is investigational to treat ependymoma.
13. **Myelodysplastic Syndromes and Myeloproliferative Neoplasms:** Allogeneic hematopoietic cell transplantation for myelodysplastic syndromes or myeloproliferative neoplasms that do not meet the criteria and guidelines are considered not medically necessary.
14. **Autoimmune Diseases:** Autologous or allogeneic hematopoietic stem-cell transplantation is considered investigational as a treatment of autoimmune diseases, including, but not limited to, the following: • multiple sclerosis (MS) • juvenile idiopathic or rheumatoid arthritis (RA) • systemic lupus erythematosus (SLE) • type 1 diabetes • chronic inflammatory demyelinating polyneuropathy.

Policy Guidelines

Refer to the individual member's benefit booklet for prior review requirements.

Acute Myeloid Leukemia (AML)
Primary refractory acute myeloid leukemia (AML) is defined as leukemia that does not achieve a complete remission after conventionally dosed (non-marrow ablative) chemotherapy. In the French-American-British (FAB) criteria, the classification of AML is solely based on morphology as determined by the degree of differentiation along different cell lines and the extent of cell maturation. The newer, currently preferred, World Health Organization (WHO) classification of AML incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers in order to construct a classification that is universally applicable and prognostically valid. The WHO system was adapted by the National Comprehensive Cancer Network (NCCN) to estimate individual patient prognosis to guide management.

For individuals who have documented cytogenetic- or molecular-documented intermediate- or poor-risk AML in first complete remission (CR1) who receive allo-HSCT with myeloablative conditioning, the evidence includes randomized controlled trials (RCTs) and matched cohort studies. Relevant outcomes are overall survival (OS) and disease-specific survival (DSS). The evidence shows allogeneic HSCT in this setting improves OS and DSS rates compared with conventional chemotherapy. All RCTs employed natural randomization based on donor availability, and an intention-to-treat analysis. Although the compiled studies used different definitions of risk categories according to various cooperative groups (eg, SWOG, Medical Research Council, European Organization for Research and Treatment of Cancer, Gruppo Italiano Malattie Ematologiche dell' Adulto), cytogenetic categories in those definitions are very similar to recent guidelines from the National Comprehensive Cancer Network (NCCN). Survival rates appear to be associated with presence of minimal residual disease and risk category. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML refractory to standard induction chemotherapy but which can be brought into first complete remission or beyond with intensified induction chemotherapy who receive allo-HSCT with myeloablative conditioning, the evidence includes retrospective data compiled from patients entered in phase 3 trials and registry data. Relevant outcomes are overall survival (OS) and disease-specific survival (DSS). The evidence would suggest allogeneic HSCT in this setting improves OS and DSS rates better than with conventional chemotherapy. Limitations of the evidence include its retrospective nature, lack of rigorous randomization, and pitfalls of registry data. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML that relapses after induction chemotherapy-induced first complete remission but which can be brought into second complete remission or beyond with intensified induction chemotherapy who receive allo-HSCT or auto-HSCT with myeloablative conditioning, the evidence includes retrospective data compiled from patients entered in phase 3 trials and registry data. Relevant outcomes are OS and DSS. The evidence has shown that allogeneic HSCT in this setting improves OS better than conventional chemotherapy. Limitations of the evidence include the retrospective nature, lack of rigorous randomization, and pitfalls of registry data. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have documented cytogenetic or molecular intermediate-or poor-risk AML in the first complete remission or beyond who for medical reasons cannot tolerate a myeloablative conditioning regimen who receive all-HSCT with reduced-intensity conditioning (RIC), the evidence includes 2 RCTs and other comparative and non-comparative studies. Relevant outcomes are OS, DSS, and treatment-related morbidity. The RCTs compared RIC with myeloablative conditioning (MAC) and reported similar rates in non-relapse mortality, relapse, and overall survival, though one of the trials was stopped early due to slow accrual of patients. Two retrospective comparative studies found no difference in overall survival or leukemia-free survival between the conditioning regimens. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML in first complete remission or beyond without a suitable allogeneic donor who receive autologous HSCT, the evidence includes prospective cohort studies in which patients with an available sibling donor were offered allogeneic HSCT (biologic randomization) with random assignment of all others to autologous HSCT or chemotherapy (or no further treatment); and randomized trials that compared autologous HSCT with chemotherapy in all patients. Relevant outcomes are OS and DSS. Compared to chemotherapy, patients undergoing auto-HSCT experienced reduced relapse and improved disease-free survival rates. Overall survival did not differ between the groups. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

Acute Lymphoblastic Leukemia (ALL)
For individuals who have childhood ALL in first complete remission (CR1) at high-risk of relapse, remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related mortality (TRM) and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, autologous HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have childhood ALL in CR1 at high-risk of relapse, remission, or refractory ALL who receive allogeneic HCT (allo-HCT), the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that allo-HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, allo-HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1, subsequent remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. Current evidence supports the use of autologous HCT for adults with high-risk ALL in CR1, whose health status is sufficient to tolerate the procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1 or subsequent remission or refractory ALL who receive allo-HCT, the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. Current evidence supports the use of myeloablative allo-HCT for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning allo-HCT may be considered for patients who demonstrate complete marrow and extramedullary first or second remission and who could be expected to benefit from a myeloablative allo-HCT, but for medical reasons would not tolerate a myeloablative conditioning regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. Evidence reviews have identified only small case series with short-term follow-up, which was considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Allo-HCT after failed autologous HCT has been shown to be of clinical benefit in other hematologic malignancies and is potentially curative. In addition, clinical input has supported the use of allo-HCT to treat relapsing ALL after a failed, prior autologous HCT, particularly with reduced-intensity conditioning regimens, in adults or children. Thus, these indications may be considered medically necessary.

Chronic Myeloid Leukemia (CML)
For individuals who have CML who receive allo-HCT, the evidence includes systematic reviews, randomized controlled trials (RCTs), and multiple prospective and retrospective series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The introduction of tyrosine kinase inhibitors (TKIs) has significantly changed the clinical use of HCT

for CML. TKIs have replaced HCT as initial therapy for patients with chronic phase CML. However, a significant proportion of cases fails to respond to TKIs, develops resistance to them, or patients cannot tolerate TKIs and proceed to allo-HCT. In addition, allo-HCT represents the only potentially curative option for those patients in the accelerated or blast phase CML. Currently available evidence has suggested that TKI pretreatment does not lead to worse outcomes if HCT is needed. Myeloablative conditioning regimens prior to HCT are used in younger (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.

For individuals who have CML who receive autologous HCT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. In the largest series (N=200 patients), median survival was 36 months for patients transplanted during an accelerated phase; median survival data were not available for patients transplanted in chronic phase. Controlled studies are needed to permit conclusions on the impact of autologous HCT on health outcomes in patients with CML. The evidence is insufficient to determine the effects of the technology on health outcomes.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning allogeneic hematopoietic cell transplantation (HCT). They 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. For patients who qualify for a myeloablative allogeneic HCT on the basis of clinical status, either a myeloablative or reduced-intensity conditioning regimen may be considered medically necessary.

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)
Risk stratification of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) guides therapy decisions, which may include hematopoietic cell transplantation for those with poor risk features. For individuals who have CLL/SLL and markers of poor-risk disease who receive allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes single-arm prospective and registry-based studies and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data suggests 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.

For individuals who have CLL/SLL who receive autologous hematopoietic cell transplantation, the evidence includes randomized controlled trials (RCTs), systematic reviews, and a TEC Assessment. 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 RCT suggests 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.

Hodgkin Lymphoma
Autologous HCT
For individuals who have Hodgkin lymphoma (HL) who receive autologous HCT as initial therapy, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid status, morbid events, treatment-related mortality, and treatment related morbidity. RCTs of autologous HCT as first-line treatment have reported that autologous HCT does not have additional benefit compared to conventional

chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed/refractory Hodgkin lymphoma who receive autologous HCT, the evidence includes randomized controlled trials (RCTs), non-randomized comparative studies, and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Two RCTs in patients with relapsed or refractory disease have reported a benefit in progression-free survival and a trend toward a benefit in overall survival. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Allogeneic HCT
For individuals who have Hodgkin lymphoma (HL) who receive allogeneic stem cell transplant (alloHCT) as first line therapy, the evidence includes no published studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No studies specifically addressing allo-HCT as first-line treatment for Hodgkin lymphoma were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory Hodgkin lymphoma who receive allo-HCT, the evidence includes several case series and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2016 meta-analysis identified 38 case series evaluating allo-HCT for relapsed or refractory Hodgkin lymphoma. Pooled analysis found a 6-month overall survival rate of 83% and a 3-year overall survival rate of 50%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed Hodgkin lymphoma after autologous HCT who receive allo-HCT, the evidence includes case series and a meta-analysis. Relevant outcomes are overall survival, disease specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2016 meta-analysis of 38 case series found that a previous autologous HCT was significantly associated with higher 1- and 2-year overall survival rates and significantly higher recurrence-free survival rates at 1 year compared with no previous autologous HCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed or refractory Hodgkin lymphoma who receive reduced-intensity conditioning (RIC) with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2015 systematic review cited a number of studies, including some with comparison groups, showing acceptable outcomes after RIC allo-HCT in patients with relapsed or refractory Hodgkin lymphoma. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Tandem Autologous HCT
For individuals who have Hodgkin lymphoma (HL) who receive tandem autologous HCT, the evidence includes nonrandomized comparative studies and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. One prospective, nonrandomized study reported that, in patients with poor prognostic markers, response to tandem autologous HCT may be higher than that for single autologous HCT. This study is not definitive due to potential selection bias, and RCTs are needed to determine the impact of tandem autologous HCT on health outcomes in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation who receive second autologous hematopoietic cell transplantation, 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.
For individuals with Hodgkin lymphoma who receive tandem autologous hematopoietic cell transplantation, 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.

Non-Hodgkin Lymphoma
Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic hematopoietic stem-cell transplant (HSCT) but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy) preclude use of a standard conditioning regimen. In patients who qualify for a myeloablative allogeneic HSCT on the basis of overall health and disease status, allogeneic HSCT using either myeloablative or RIC may be considered. However, a myeloablative conditioning regimen with allogeneic HSCT may benefit younger patients with good performance status and minimal comorbidities more than allogeneic HSCT with RIC.

No randomized studies have been conducted on the use of tandem HSCT for the treatment of non-Hodgkin lymphoma (NHL) and the published evidence comprises small numbers of patients. Due in part to the relative rarity of the disease, randomized studies on the use of HSCT in mantle cell lymphoma (MCL) have not been conducted.

Plasma Cell Dyscrasias, Multiple Myeloma, POEMS Syndrome
Newly Diagnosed Multiple Myeloma
For individuals who have newly diagnosed multiple myeloma who receive autologous hematopoietic cell transplantation (HCT) as initial treatment, includes several prospective, randomized controlled trials (RCTs) that compared conventional chemotherapy with high-dose chemotherapy with autologous HCT. Relevant outcomes include overall survival (OS) and treatment-associated morbidity. In general, the evidence suggests OS rates are improved with autologous HCT compared with conventional chemotherapy in this setting. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have newly diagnosed multiple myeloma who receive tandem autologous HCT, the evidence includes several RCTs. Relevant outcomes include overall survival and treatment-related morbidity. Compared with single autologous HCT, a number of RCTs demonstrated tandem autologous HCT improved OS and recurrence-free survival in newly diagnosed multiple myeloma. The available RCTs compare RIC allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on “genetic randomization,” ie, patients with a human leukocyte antigen-identical sibling who were offered an RIC allo-HCT following autologous HCT, whereas other patients underwent either 1 or 2 autologous transplants. Although the body of evidence has shown inconsistencies in terms of overall survival and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allogeneic HCT, although at a cost of higher transplant-related mortality compared with conventional treatments. Factors across studies that may account for differing trial results include different study designs, nonuniform preparative regimens, different patient characteristics (including risk stratification), and criteria for advancing to a second transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have newly diagnosed multiple myeloma who receive allogeneic HCT (allo-HCT) with as initial or salvage treatment, the evidence includes nonrandomized studies. Relevant outcomes include overall survival and treatment-related morbidity. Studies have reported on patients with both myeloablative and RIC conditioning. Limitations of the published evidence include patient sample heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes, and inconsistency in reporting or collecting outcomes. Nonmyeloablative

allo-HCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allo-HCT improves survival better than autologous HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Relapsed or Refractory Multiple Myeloma
For individuals who have relapsed multiple myeloma who receive autologous HCT after failing an autologous HCT, the evidence includes 1 RCT and a systematic review summarizing data from 4 series of patients who relapsed after a first autologous HCT. Relevant outcomes include overall survival and treatment-related morbidity. Despite some limitations of the published evidence, including patient sample heterogeneity, variability in treatment protocols, and short follow-up periods, the available trial evidence has suggested overall survival rates are improved with autologous HCT compared with conventional chemotherapy in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory multiple myeloma who receive tandem autologous HCT after failing the first transplant, the evidence includes 3 RCTs. Relevant outcomes include overall survival and treatment-related morbidity. The evidence has shown tandem autologous HCT improves overall survival rates in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POEMS Syndrome
The evidence for HCT of any type in patients who have POEMS syndrome includes case reports and series. Relevant outcomes include OS and treatment-related morbidity. No RCTs of HCT of any type have been performed in patients with POEMS syndrome of any severity, nor is it likely such studies will be performed because of the rarity of this condition. Available case reports and series are subject to selection bias and are heterogeneous with respect to treatment approaches and peri-transplant support.

Waldenstrom Macroglobulinemia
For individuals who have Waldenstrom macroglobulinemia who receive hematopoietic cell transplantation (HCT), the evidence includes case series. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Several retrospective series have evaluated HCT for Waldenstrom macroglobulinemia. Analyses of registry data found an overall survival rate of 52% at 5 years after allogeneic HCT and 68.5% after autologous HCT. The total number of patients studied was small and there is a lack of published controlled studies. The evidence is insufficient to determine the effects of the technology on health outcomes.
Clinical input and national and international clinical guidelines support the use of autologous HCT as salvage therapy for chemosensitive Waldenstrom macroglobulinemia. Allogeneic HCT is recommended in the context of clinical trials. Thus, autologous HCT may be considered medically necessary as salvage therapy for chemosensitive Waldenstrom macroglobulinemia and allogeneic HCT for Waldenstrom macroglobulinemia is considered investigational. The 2016 National Comprehensive Cancer Network (NCCN) guidelines indicate that selected cases of Waldenstrom's macroglobulinemia may be treated with autologous or allogeneic HSCT but the latter only in a clinical trial.

Miscellaneous Solid Tumors in Adults
For individuals who have adult soft tissue sarcomas who receive HCT, the evidence includes 2 TEC Assessments, 1 randomized controlled trial (RCT) and several phase 2 single arm studies, a number of which have been summarized in a Cochrane review. Relevant outcomes include overall survival, disease specific survival, and treatment related morbidity and mortality. 1995 and 1999 TEC Assessments focusing on HCT as primary and salvage therapy for a variety of solid tumors found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Although 1 small phase 2 study reported longer survival for patients treated with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have small cell lung cancer (SCLC) who receive HCT, the evidence includes 2 TEC Assessments, several RCTs, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and

1999 TEC Assessments, focusing on HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Studies published since the TEC Assessments have not reported increased overall survival for patients with SCLC treated with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive HCT, the evidence includes a TEC Assessment and small single-arm series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Since publication of the TEC Assessments, the evidence for HCT to treat adult soft tissue sarcomas, renal cell carcinoma, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to small case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

Solid Tumors of Childhood
Neuroblastoma
• The use of single autologous HSCT has become a widely accepted treatment option for children with "high-risk" neuroblastoma, after randomized studies have shown improved event-free survival (EFS) and overall survival (OS).
• No studies directly comparing single autologous to tandem autologous HSCT for high-risk neuroblastoma have been published; however, case series on the use of tandem autologous for high-risk neuroblastoma have reported EFS rates superior to those reported with the use of single autologous HSCT (reported in randomized trials comparing single autologous HSCT to conventional chemotherapy). Some transplant centers use tandem autologous HSCT as the preferred approach to the treatment of high-risk neuroblastoma. A Phase III, randomized trial of single versus tandem autologous HSCT for high-risk neuroblastoma is currently underway.
There are varied results for a survival benefit with the use of HSCT for the following conditions:
1)Ewing's sarcoma family of tumors (ESFT). Two Phase III trials are currently underway using risk-stratified approaches which will likely serve to guide future treatment options for ESFT.
2)Rhabdomyosarcoma
3)Wilms tumor. A Phase II trial is currently underway using a risk-stratified approach to treatment and includes high-risk patients who will be treated with HSCT.
4)Osteosarcoma. The use of HSCT for osteosarcoma has failed to show a survival benefit.
5)Retinoblastoma • Small case series and case reports have shown prolonged disease-free survival (DFS) in some patients with stage 4 retinoblastoma, particularly those with stage 4a disease. • A recent study of 15 patients showed that some patients with stage 4a disease were cured with the use of HSCT. A prospective multicenter trial (COG ARET 0321) is underway to better determine the role of HSCT in patients with retinoblastoma.

Allogeneic HSCT
Very little evidence is available on the use of allogeneic HSCT for pediatric solid tumors, either upfront or as salvage therapy after a failed autologous HSCT. A large retrospective review of the use of allogeneic HSCT for high-risk neuroblastoma failed to show a survival benefit over autologous HSCT and was associated with a higher risk of transplant-related mortality.

Germ Cell Tumors
For individuals who have previously untreated germ cell tumors who receive first-line treatment with autologous HCT, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available trials found after autologous HCT as initial therapy for g erm cell tumors did not significantly improve outcomes compared with alternative therapy (eg, standard-dose chemotherapy). Study sample sizes were relatively small and may have been underpowered to detect differences between groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes 1 RCT and several case series. Relevant outcomes are overall survival, disease specific survival, and treatment-related mortality and morbidity. The RCT did not find significant differences in outcomes between autologous HCT plus high-dose chemotherapy and standard-dose chemotherapy. Case series found 3-year overall survival rates that ranged from 55% to 60%; these studies lacked comparison groups. The evidence is insufficient to determine the effects of the technology on health outcomes. 5- year survival outcomes did not differ significantly between groups. Overall, the available studies have included heterogeneous patient populations, in different salvage treatment settings (ie, first vs subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system to risk stratify patients. Tandem or sequential HCT has not shown benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. There were no RCTs or non-RCTs evaluating allogeneic HCT for germ cell tumors. One 2007 case report described successful treatment of a refractory mediastinal gem cell tumor with allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

CNS Embryonal Tumors and Ependymoma

For individuals who have newly diagnosed central nervous system (CNS) embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. In the case of pediatric CNS embryonal tumors, an important consideration is whether the use of HCT may allow for a reduction in radiation dose. Data from single-arm studies using HDC with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both event-free survival and overall survival) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly in patients with disease that is considered high risk. In a retrospective comparative study, survival in patients receiving HDC with HCT and delayed craniospinal irradiation was comparable to survival in those receiving upfront craniospinal irradiation. Overall, data from these observational studies has suggested HCT may allow reduced doses of craniospinal irradiation without worsening survival outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent/relapsed CNS embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective single-arm studies and a systematic review of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT are variable, and survival is generally very poor for tumors other than medulloblastoma. Data from some single-arm studies using autologous HCT to treat recurrent CNS embryonal tumors have shown comparable or improved survival compared with historical controls treated with conventional therapy for certain patients. The results of a 2012 systematic review of observational studies in patients with relapsed supratentorial primitive neuroectodermal tumor (sPNET) suggested that a subgroup of infants with chemosensitive disease might benefit from autologous HCT, achieving survival without the use of radiotherapy, whereas outcomes in older children and/or in pineal location are poor with this modality. However, a relatively large prospective multicenter study has reported that HCT was not associated with improved survival outcomes in patients who had a good response to therapy. Overall, data from these single-arm studies has suggested HCT may be associated with improved survival outcomes in select patients, although data for some tumor types is limited (eg, atypical teratoid/rhabdoid tumors). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have ependymoma who receive autologous HCT, the evidence includes relatively small case series. Relevant outcomes are overall survival, disease-specific survival, and treatment

related morbidity and mortality. The available case series do not report higher survival rates for patients with ependymoma treated with HCT than with standard therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Allogeneic HCT for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
For individuals who have MDS and MPN who receive myeloablative conditioning allo-HCT, the evidence includes case series, which are often heterogeneous in terms of diseases included. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Primarily uncontrolled, observational studies of HCT for MDS report a relatively large range of overall and progression-free survival values, which reflects the heterogeneity in patient populations, conditioning regimens, and other factors. Reported estimates for 3- to 5-year overall survival of approximately 40% to 50% are typical. For HSCT for MPN, data are more limited. At least 1 comparative study of HCT for myelofibrosis demonstrated improved survival with HCT compared with standard therapy. HCT is at present the only potentially curative treatment option for patients with MDS and MPN. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have MDS and MPN who receive reduced-intensity conditioning allo-HCT, the evidence includes randomized controlled trials and retrospective observational series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Evidence from randomized controlled trials and retrospective nonrandomized comparisons suggests that RIC may be used as a risk-adapted strategy in high-risk patients who are older and with more comorbidities without significantly worsening overall survival. RIC appears to be associated with lower rates of non-relapse mortality but higher cancer relapse than myeloablative HCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Allogeneic HCT for Genetic Diseases and Acquired Anemia
The following immunodeficiencies have been successfully treated by allogeneic HCT: Lymphocyte immunodeficiencies • Adenosine deaminase deficiency • Artemis deficiency • Calcium channel deficiency • CD 40 ligand deficiency • Cernunnos/X-linked lymphoproliferative disease deficiency • CHARGE syndrome with immune deficiency • Common gamma chain deficiency • Deficiencies in CD 45, CD3, CD8 • DiGeorge syndrome • DNA ligase IV • Interleuken-7 receptor alpha deficiency • Janus-associated kinase 3 (JAK3) deficiency • Major histocompatibility class II deficiency • Omenn syndrome • Purine nucleoside phosphorylase deficiency • Recombinase-activating gene (RAG) 1/2 deficiency • Reticular dysgenesis •Winged helix deficiency • Wiskott-Aldrich syndrome • X-linked lymphoproliferative disease • Zeta-chain-associated protein-70 (ZAP-70) deficiency
Other immunodeficiencies • Autoimmune lymphoproliferative syndrome • Cartilage hair hypoplasia • CD25 deficiency • Hyper IgD and IgE syndromes • ICF syndrome • IPEX syndrome • NEMO deficiency • NF-κB inhibitor, alpha (IκB-alpha) deficiency • Nijmegen breakage syndrome. In the inherited metabolic disorders, allogeneic HSCT has been proven effective in some cases of Hurler, Maroteaux-Lamy, and Sly syndromes, childhood onset cerebral X-linked adrenoleukodystrophy, globoid-cell leukodystrophy, metachromatic leukodystrophy, alphamannosidosis, and aspartylglucosaminuria. Allogeneic HSCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM1, gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HSCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes.

Autoimmune Diseases
For individuals with systemic sclerosis/scleroderma who receive HSCT, the evidence includes 3 RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. All three RCTs compared cyclophosphamide conditioning plus autologous HCT with cyclophosphamide alone. Patients in the RCTs were adults (up to 69 years of age in one trial), maximum duration of disease of 5 years, with modified Rodnan skin scores >15, and internal organ involvement. Patients with severe and irreversible organ involvement were excluded from the trials. Short-term results of the RCTs showed higher rates

of adverse events and transplant-related mortality among patients receiving autologous HCT compared with patients receiving chemotherapy alone. However, long-term improvements (four years) in clinical outcomes such as modified Rodnan skin scores and forced vital capacity, as well as overall mortality in patients receiving HCT compared with patients receiving cyclophosphamide alone, were consistently reported in all RCTs. Due to sample size limitations in two of the RCTs, statistical significance was found only in the larger RCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

For individuals with multiple sclerosis who receive HSCT, the evidence includes a randomized controlled trial (RCT) and several case series. Relevant outcomes are overall survival, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. The phase 2 RCT compared HSCT to mitoxantrone and reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HSCT developed significantly fewer lesions than the group receiving conventional therapy. Findings of case series showed improvements in clinical parameters following HSCT compared to baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials with appropriate comparator therapies that report on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have juvenile idiopathic or rheumatoid arthritis who receive HSCT, the evidence includes registry data and a case series. Relevant outcomes are symptoms, quality of life, medication use, treatment-related mortality, and treatment-related morbidity. The registry study included 50 patients and the overall drug-free remission rate was approximately 50% in the registry patients and 69% in the smaller case series. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with systemic lupus erythematosus who receive HSCT, the evidence includes a systemic review and case series. Relevant outcomes are overall survival, symptoms, quality of life, treatment-related mortality, and treatment-related morbidity. Studies were heterogeneous in conditioning regimens and source of cells. The largest series (N=50 patients) found an overall 5-year survival rate of 84% and the probability of disease-free survival was 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with type 1 diabetes who receive HSCT, the evidence includes case series and a meta-analysis of 22 studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. While a substantial proportion of patients tended to become insulin free after HSCT, remission rates were high. The meta-analysis further revealed that HCT is more effective in patients with type 1 diabetes compared with type 2 diabetes and when HCT is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT in treating diabetes. Those factors are heterogeneity in the stem cell types, cell number infused, and infusion methods. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Amyloidosis
For individuals who have primary amyloidosis who receive autologous hematopoietic cell transplantation (HCT), the evidence includes a randomized controlled trial (RCT), nonrandomized comparative studies, and large case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloidogenic light chain (AL) produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. Complete response to treatment has been reported in 34% to 66% of patients, while transplant-related mortality rates have declined, from as high as 40% to less than 14% in current studies. Therefore, autologous HCT is an important option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary amyloidosis who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Evidence on the use of allogeneic HCT is sparse, and the available evidence shows high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

Epithelial Ovarian Cancer
The use of hematopoietic cell transplantation (HCT) has been investigated for treatment of patients with epithelial ovarian cancer. Hematopoietic stem cells are infused to restore bone marrow function after cytotoxic doses of chemotherapeutic agents with or without whole body radiotherapy.

For individuals who have advanced-stage epithelial ovarian cancer who receive HCT, the evidence includes randomized trials and data from case series and registries. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment related mortality and morbidity. Although some observational studies have reported longer survival in subsets of women with advanced epithelial ovarian cancer than in women treated with standard chemotherapy, none of the randomized trial evidence has shown a benefit from HCT in this population. Overall, the evidence has not shown that HCT improves health outcomes in treating epithelial ovarian cancer, including survival, compared with conventional standard doses of chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Medical Director review 8/2024

Policy Implementation/Update Information

10/27/20 New policy developed. Combined all HCT policies into one policy for efficiency. Code review completed. Medical Director review 10/2020. (lpr)

12/8/20 Specialty Matched Consultant Advisory panel review 11/18/2020. No change to policy statement. (lpr)

9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. References added. Added Related Policies section. No change to policy statement. (lpr)

3/22/22 References added. (lpr)

9/13/22 Specialty Matched Consultant Advisory Panel review 8/24/22. No change to policy statement. (lpr)

9/12/23 Specialty Matched Consultant Advisory Panel review 8/16/2023. References added. (lpr)

9/18/24 Specialty Matched Consultant Advisory Panel review 8/21/2024. References added. No change to policy statement. (lpr)