



Medical Coverage Policy

Effective Date1/15/2024

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Coverage Policy Number..... 0534

Stem Cell Transplantation: Solid Tumors

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Related Coverage Resources

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- [Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell \(HPC\) Boost](#)
- [Stem Cell Transplantation: Blood Cancers](#)
- [Stem Cell Transplantation: Non-cancer Disorders](#)
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for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses hematopoietic stem cell transplantation (HSCT) for adult and pediatric solid tumor cancers.

Coverage Policy

Coverage for hematopoietic stem cell transplantation (HSCT) varies across plans. Refer to the customer’s benefit plan document for coverage details.

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
Central Nervous System (CNS) Tumors	<p>Autologous HSCT is considered as medically necessary for the treatment of the following central nervous system tumors:</p> <ul style="list-style-type: none"> • supratentorial primitive neuroectodermal tumor (PNET) • medulloblastoma <p>Autologous HSCT is considered experimental, investigational or unproven for the treatment of ANY of the following central nervous system tumors:</p> <ul style="list-style-type: none"> • anaplastic glioma • astrocytoma • ependymoma • glioblastoma • meningioma • oligodendroglioma • primary spinal cord tumors <p>Allogeneic HSCT is considered experimental, investigational or unproven for the treatment of central nervous system tumors.</p>
Ewing Family of Tumors	<p>Autologous HSCT is considered medically necessary for the treatment of relapsed or progressive Ewing family of tumors.</p>
Germ Cell Tumors (e.g., testicular)	<p>Single or tandem autologous HSCT is considered medically necessary for relapsed or refractory testicular and ovarian germ cell tumors.</p> <p>Up to three autologous HSCT is considered medically necessary as second-line therapy for metastatic germ cell tumors.</p> <p>EITHER of the following procedures for the treatment of testicular cancer is considered experimental, investigational or unproven:</p> <ul style="list-style-type: none"> • autologous HSCT as front-line therapy • allogeneic HSCT

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
Neuroblastoma	<p>Autologous HSCT is considered medically necessary for the treatment of high-risk neuroblastoma.</p> <p>Allogeneic HSCT is considered medically necessary for the treatment of high-risk neuroblastoma when the individual is not a candidate for autologous HSCT.</p> <p>A maximum of three tandem autologous HSCTs is considered medically necessary for the treatment of high-risk neuroblastoma.</p>
Retinoblastoma	Autologous HSCT is considered medically necessary for the treatment of retinoblastoma.
Wilms Tumor	Autologous HSCT is considered medically necessary for the treatment of relapsed Wilms tumor.
Adult - Other	<p>HSCT for the treatment of ANY of the following solid tumors in an adult is considered experimental, investigational and unproven:</p> <ul style="list-style-type: none"> • cancer of the bile duct • cancer of the breast • cancer of the cervix • cancer of the colon and rectum • cancer of the esophagus • cancer of the gallbladder • cancer of the lung • cancer of the nasopharynx • cancer of the pancreas • cancer of the paranasal sinus • cancer of the prostate • cancer of the stomach (gastric cancer) • cancer of the thymus • cancer of the thyroid • cancer of the uterus • epithelial ovarian cancer • melanoma • renal cell carcinoma • soft tissue sarcoma

General Background

Hematopoietic stem cell transplantation (HSCT), also called hematopoietic cell transplantation (HCT) or stem cell transplant, is a type of treatment for cancer (and a few other conditions as well). Bone marrow produces all of the different cells that make up the blood, such as red blood cells, white blood cells, and platelets. All of the cells of the immune system are also made in the bone marrow. All of these cells develop from a type of precursor cell found in the bone marrow, called a "hematopoietic stem cell." Hematopoietic stem cells are found in the peripheral blood and the bone marrow; therefore stem cells can be collected or harvested from either location.

Some of the most effective treatments for cancer, such as chemotherapy and radiation, are toxic to the bone marrow. In general, the higher the dose, the more toxic the effects on the bone marrow. After the treatment, a healthy supply of stem cells is reintroduced, or transplanted. The transplanted cells then reestablish the blood cell production process in the bone marrow. HSCT is

a method of replacing immature blood-forming cells in the bone marrow that have been destroyed by drugs, radiation, or disease. It may be autologous (i.e., using a person's own stem cells) or allogeneic (i.e., using stem cells donated by someone else).

- Autologous transplant — In autologous transplantation, an individual's own hematopoietic stem cells are removed before the high dose chemotherapy or radiation is given, and they are then frozen for storage and later use. After chemotherapy or radiation is complete, the harvested cells are thawed and returned to the individual, like a transfusion.
- Allogeneic transplant — In allogeneic transplantation, the hematopoietic stem cells come from a donor, ideally a brother or sister with a similar genetic makeup. If an individual does not have a suitably matched sibling, an unrelated person with a similar genetic makeup may be used. Under some circumstances, a parent or child who is only half-matched can also be used; this is termed a haploidentical transplant. In other circumstances, umbilical cord blood may be used in an umbilical cord blood transplant.
- Myeloablative transplant — A myeloablative transplantation uses very high doses of chemotherapy or radiation prior to transplantation with autologous or allogeneic hematopoietic stem cells.
- Non-myeloablative transplant — A non-myeloablative transplantation, sometimes referred to as reduced intensity transplant, allows an individual to have less intensive chemotherapy before transplantation with allogeneic hematopoietic stem cells. The idea is to minimize up front toxicity by using lower doses of intensive therapy, while retaining the immune graft versus tumor effect. This approach may be recommended for a variety of reasons including age, type of disease, other medical issues, or prior therapies.

Contraindications

Many factors affect the outcome of a tissue transplantation; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications for HSCT include (but are not limited to):

- poor cardiac function (ejection fraction less than 35%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal), unless related to disease
- poor renal function (creatinine clearance less than 50 mL/min) (not applicable for most auto transplants)
- poor pulmonary function (diffusion capacity less than 50% of predicted), human immunodeficiency virus (HIV) if not controlled, active hepatitis B, hepatitis C, or human T-cell lymphotropic virus type 1 (HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

Bone Cancer

True (or primary) bone tumors start in the bone itself and may include:

- Osteosarcoma (also called osteogenic sarcoma) is the most common primary bone cancer. It starts in the bone cells. It most often occurs in young people between the ages of 10 and 30, but about 10% of osteosarcoma cases develop in people in their 60s and 70s.
- Chondrosarcoma
- Ewing tumor/Ewing sarcoma is rare in adults older than 30
- Malignant fibrous histiocytoma (MFH) most often starts in soft tissue (connective tissues such as ligaments, tendons, fat, and muscle); it's rare in bones. This cancer is also known as pleomorphic undifferentiated sarcoma, especially when it starts in soft tissues. This cancer most often occurs in elderly and middle-aged adults. It's quite rare in children.

Central Nervous System (CNS) Tumors

Primary central nervous system (CNS) tumors are a diverse group of tumors originating in the brain or spinal cord. CNS tumors develop from different cell types and form in different areas of the CNS. CNS tumors are more common in children than adults and constitute the most common solid tumors of childhood.

- Tumor location: The brain is divided into two compartments by the tentorium. Above the tentorium (supratentorial) are the cerebral hemispheres, basal ganglia, and the thalamus. Below the tentorium (infratentorial) are the pineal gland, the tectum, the pons, the medulla, and the cerebellum. Adult brain tumors tend to be supratentorial; however, pediatric tumors are evenly split between supratentorial and infratentorial. This division of location in the pediatric population is dependent on the age of the patient.
- Tumor type: Some CNS tumor types include astrocytoma/oligodendroglioma, anaplastic glioma/glioblastoma, adult intracranial and spinal ependymoma, adult medulloblastoma, primary spinal cord tumors, and meningiomas. Cranial primitive neuroectodermal tumors (PNET) are embryonal neoplasms showing varying degrees of differentiation. They are described by their location as infratentorial (medulloblastomas) and supratentorial (cerebral neuroblastoma, pineoblastoma, esthesioneuroblastoma).

Germ Cell Tumors (GCTs)

Germ cell tumors are growths that form from reproductive cells. Tumors may be cancerous or noncancerous. Most germ cell tumors that are cancerous occur as either cancer of the ovaries (ovarian cancer) or cancer of the testicles (testicular cancer).

- Testicular cancer: More than 90% of cancers of the testicle start in cells known as germ cells. These are the cells that make sperm. The main types of GCTs in the testicles are seminomas and non-seminomas. These types occur about equally. Seminomas tend to grow and spread more slowly than non-seminomas. Non-seminomas usually occur in men between their late teens and early 30s. Many testicular cancers contain both seminoma and non-seminoma cells.
- Ovarian: Germ cell tumors start from the cells that produce the eggs (ova). Less than 2% of ovarian cancers are germ cell tumors.

Neuroblastoma

Neuroblastoma starts in certain, very early forms of nerve cells, most often found in an embryo or fetus. This type of cancer occurs most often in infants and young children. It is rare in children older than 10 years. Neuroblastoma treatment depends on risk groups determined by-cancer staging, the age of the child, tumor histology, and tumor biology.

Ovarian Cancer

The ovaries are mainly made up of 3 kinds of cells. Each type of cell can develop into a different type of tumor:

- Epithelial ovarian tumors start from the cells that cover the outer surface of the ovary. Most ovarian tumors are epithelial cell tumors. These tumors can be benign (not cancer), borderline (low malignant potential), or malignant (cancer). About 90% of malignant ovarian cancers are epithelial ovarian carcinomas.
- Germ cell tumors start from the cells that produce the eggs (ova). Less than 2% of ovarian cancers are germ cell tumors.
- Stromal tumors start from structural tissue cells that hold the ovary together and produce the female hormones estrogen and progesterone.

Some of these tumors are benign (non-cancerous) and never spread beyond the ovary. Malignant (cancerous) or borderline (low malignant potential) ovarian tumors can spread (metastasize) to other parts of the body and can be fatal.

Retinoblastoma

Retinoblastoma is a cancer that starts in the retina, the very back part of the eye. It is the most common type of eye cancer in children.

Soft Tissue Sarcoma

Bone and soft tissue sarcomas are the main two types of sarcoma. Soft tissue sarcomas can develop in soft tissues like fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues. They can be found in any part of the body.

- Rhabdomyosarcoma is the most common type of soft tissue sarcoma seen in children.

In a review on racial disparities related to hematopoietic stem cell transplantation (HSCT), Majhail, et al. (2012) indicated that HSCT is a specialized, high-cost, and resource-intensive procedure associated with racial disparities. The authors point to the following conclusions drawn from several studies that have addressed race and access to HSCT:

- Blacks are less likely than whites to receive HSCT.
- There is no association of race and outcomes for autologous HSCT; Black allogeneic HSCT recipients had higher risks of mortality compared with whites; and the effect of race was independent of socioeconomic status.
- Blacks had a shorter progression free survival compared with whites after autologous HSCT for multiple myeloma; this study did not account for socioeconomic status.
- Black allogeneic matched unrelated donor recipients had worse overall survival, disease free survival, and higher treatment related mortality than whites; the effect of race was independent of socioeconomic status.
- Blacks had worse overall survival compared with whites after single umbilical cord blood HSCT; the study did not account for socioeconomic status.

The authors cite several reasons for these disparities including donor availability and access to HSCT. In those patients who require allogeneic HSCT, there is a need for appropriately HLA-matched donors which has a much higher likelihood if the individuals are of the same race. According to the National Marrow Donor Program, 74% of donors are white, 10% are Hispanic, 7% are Black, and 7% are Asian. As such, the "probability of finding a match within the registry is estimated to be 0.93 for whites, 0.82 for Hispanics, 0.77 for Asian Americans, and 0.58 for Blacks." Black patients with leukemia and lymphoma were 51-53% and 34-45% as likely, respectively, to receive HSCT compared to whites ($p < 0.05$). Compared with private insurance, Medicaid patients were also less likely to receive HSCT. For all diseases, whites were significantly more likely than Blacks to receive HSCT ($p < 0.0001$). This review highlights the need for additional research to better understand the factors contributing to these racial disparities and to develop interventions to eliminate them.

Similar findings were presented in a 2021 systematic review ($n=40$) of retrospective cohort studies, literature reviews, longitudinal studies, cross-sectional studies, and focus group samplings that aimed to summarize racial disparities related to HSCT referral, utilization, and survival. The author pointed to "discouragement of potential donors, differences in treatment failure and/or transplant rejection, and overall stigmatization and mistrust of the medical profession" as significant reasons for the worse outcomes that are seen in minority patients (Landry, 2021).

Professional Societies/Organizations

The table below includes information and recommendations from the following sources:

1. The American Society for Transplantation and Cellular Therapy (ASTCT) Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy (Kanate, et al., 2020).
2. The National Comprehensive Cancer Network® (NCCN) NCCN GUIDELINES™ Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. Note that all recommendations are category 2A unless otherwise stated.
3. The National Cancer Institute (NCI) Physician Data Query (PDQ®) Health Professional Version documents.

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Bone	<p><u>American Society for Transplantation and Cellular Therapy (2020)</u> (CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="background-color: #cccccc;">Children (<18 years)</th> <th style="background-color: #cccccc;">Allogeneic HCT</th> <th style="background-color: #cccccc;">Autologous HCT</th> </tr> </thead> <tbody> <tr> <td>Ewing's sarcoma, high risk or relapse</td> <td>D</td> <td>S</td> </tr> <tr> <td>Osteosarcoma, high risk</td> <td>N</td> <td>C</td> </tr> </tbody> </table> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="background-color: #cccccc;">Adults</th> <th style="background-color: #cccccc;">Allogeneic HCT</th> <th style="background-color: #cccccc;">Autologous HCT</th> </tr> </thead> <tbody> <tr> <td>Ewing's sarcoma, high risk</td> <td>D</td> <td>C</td> </tr> </tbody> </table> <p><u>NCCN GUIDELINES™ Bone cancer (v.1.2024, August 7, 2023)</u> <u>Ewing sarcoma</u> “High-dose therapy followed by stem cell transplant (HDT/SCT) has been evaluated in patients with localized as well as metastatic disease. HDT/SCT has been associated with potential survival benefit in patients with non-metastatic disease. However, studies that have evaluated HDT/SCT in patients with primary metastatic disease have shown conflicting results.” (MS-17)</p> <p><u>Ewing sarcoma - Relapsed or Refractory Disease</u> “HDT/SCT has been associated with long-term survival in patients with relapsed or progressive Ewing sarcoma in small single-institution studies. The role of this approach is yet to be determined in prospective randomized studies.” (MS-20)</p> <p><u>Osteosarcoma - Relapsed or Refractory Disease</u> “The safety and efficacy of HDT/SCT in patients with locally advanced, metastatic, or relapsed osteosarcoma have also been evaluated.” “The efficacy of this approach in patients with high-risk disease is yet to be determined in prospective randomized studies (MS-31)</p> <p><u>NCI Ewing Sarcoma and Undifferentiated Small Round Cell Sarcomas of Bone and Soft Tissue Treatment (PDQ®) August 25, 2023</u> Treatment options for localized Ewing sarcoma include:</p>	Children (<18 years)	Allogeneic HCT	Autologous HCT	Ewing's sarcoma, high risk or relapse	D	S	Osteosarcoma, high risk	N	C	Adults	Allogeneic HCT	Autologous HCT	Ewing's sarcoma, high risk	D	C
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	<ul style="list-style-type: none"> • "Chemotherapy • Local-control measures: <ul style="list-style-type: none"> ◦ Surgery ◦ Radiation therapy • High-dose chemotherapy with autologous stem cell rescue." <p>Treatment options for recurrent Ewing sarcoma include:</p> <ul style="list-style-type: none"> • "Chemotherapy • Surgery • Radiation therapy • High-dose chemotherapy with stem cell support • Other therapies." 									
Breast	<p><u>American Society for Transplantation and Cellular Therapy (2020)</u> (N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)</p> <table border="1" data-bbox="448 806 1295 940"> <thead> <tr> <th data-bbox="448 806 928 869">Adults</th> <th data-bbox="928 806 1107 869">Allogeneic HCT</th> <th data-bbox="1107 806 1295 869">Autologous HCT</th> </tr> </thead> <tbody> <tr> <td data-bbox="448 869 928 905">Breast cancer, adjuvant high risk</td> <td data-bbox="928 869 1107 905">N</td> <td data-bbox="1107 869 1295 905">N</td> </tr> <tr> <td data-bbox="448 905 928 940">Breast cancer, metastatic</td> <td data-bbox="928 905 1107 940">D</td> <td data-bbox="1107 905 1295 940">N</td> </tr> </tbody> </table> <p>No mention of stem cell transplant in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer v.4.2022, June 21, 2022.</p> <p>No mention of stem cell transplant in the National Cancer Institute (NCI) Breast Cancer Treatment (Adult) (PDQ®)–Health Professional Version (Updated: September 28, 2022).</p>	Adults	Allogeneic HCT	Autologous HCT	Breast cancer, adjuvant high risk	N	N	Breast cancer, metastatic	D	N
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	<p>in patients who achieve a CR with conventional doses of systemic therapy or have no residual disease after re-resection." (AMED-A)</p> <p><u>Adult Medulloblastoma</u> "In the setting of recurrence, several regimens are in use in the recurrence setting, most of which include etoposide. Temozolomide has also been used in this setting. High-dose chemotherapy in combination with autologous stem cell transplantation is a feasible strategy for patients who have had good response with conventional-dose chemotherapy, although long-term control is rarely achieved." "Collection of stem cells before RT may be considered on the condition that RT is not delayed for potential future autologous stem cell reinfusion at disease progression." (MS-25)</p> <p><u>Adult Medulloblastoma - Recurrence and Progression</u> "High-dose chemotherapy with autologous stem cell rescue may be considered for patients showing no evidence of disease after conventional reinduction chemotherapy." (MS-26)</p> <p><u>NCI Childhood Astrocytoma's Treatment (PDQ®) April 19, 2022</u> Treatment options for recurrent childhood high-grade astrocytoma's include:</p> <ul style="list-style-type: none"> • "Surgery (not considered standard treatment) • High-dose chemotherapy with stem cell transplant (SCT) (not considered standard treatment) • Radiation therapy (not considered standard treatment) • Targeted therapy with a BRAF inhibitor, for patients with a BRAF V600E mutation (not considered standard treatment) • Immunotherapy (not considered standard treatment)" <p><u>NCI Childhood Brain Stem Glioma Treatment (PDQ®) February 23, 2022</u> <u>Standard Treatment Options for Newly Diagnosed Diffuse Intrinsic Pontine Gliomas (DIPGs)</u> "Standard treatment options for newly diagnosed childhood DIPGs include radiation therapy. No chemotherapeutic (including neoadjuvant, concurrent, post radiation chemotherapy) or immunotherapy strategy, when added to radiation therapy, has led to long-term survival for children with DIPGs. This includes therapy using high-dose, marrow-ablative chemotherapy with autologous hematopoietic stem cell rescue, which has been shown to be ineffective in extending survival."</p> <p><u>NCI Childhood Medulloblastoma and Other Central Nervous System Embryonal Tumors Treatment (PDQ®) April 12, 2023</u> <u>Treatment of Childhood Pineoblastoma, Treatment of children aged 3 years and younger</u> "Standard treatment options for children aged 3 years and younger with pineoblastoma include the following:</p> <ul style="list-style-type: none"> • Biopsy (for diagnosis) and subtotal resection, if possible. • Adjuvant chemotherapy.

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	<ul style="list-style-type: none"> • High-dose, marrow-ablative chemotherapy with autologous bone marrow rescue or peripheral stem cell rescue.” <p><u>Treatment of Recurrent Childhood Medulloblastoma and Other CNS Embryonal Tumors</u> “There are no standard treatment options for recurrent childhood CNS embryonal tumors.” “For most children, treatment is palliative, and disease control is transient in patients previously treated with radiation therapy and chemotherapy, with more than 80% of patients progressing within 2 years. For young children, predominantly those younger than 3 years at diagnosis who were never treated with radiation therapy, longer-term control with reoperation, radiation therapy, and chemotherapy is possible. Treatment approaches may include the following:</p> <ul style="list-style-type: none"> • Surgery. • Radiation therapy. • Chemotherapy. • High-dose chemotherapy with stem cell rescue. • Molecularly targeted therapy.” <p><u>NCI Childhood Central Nervous System Germ Cell Tumors (GCT) Treatment (PDQ®) August 22, 2023</u> “Treatment options for recurrent childhood CNS GCTs include the following:</p> <ul style="list-style-type: none"> • Chemotherapy followed by additional radiation therapy. • High-dose chemotherapy with stem cell rescue with or without additional radiation therapy.” <p><u>NCI Childhood Ependymoma Treatment (PDQ®) June 7, 2023</u> Treatment of residual disease, no disseminated disease: “There is no evidence that high-dose chemotherapy with stem cell rescue is of any benefit.”</p>																		
Germ Cell Tumors	<p><u>American Society for Transplantation and Cellular Therapy (2020)</u> (CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</p> <table border="1" data-bbox="448 1383 1295 1520"> <thead> <tr> <th>Children (<18 years)</th> <th>Allogeneic HCT</th> <th>Autologous HCT</th> </tr> </thead> <tbody> <tr> <td>Germ cell tumor, relapse</td> <td>D</td> <td>C</td> </tr> <tr> <td>Germ cell tumor, refractory</td> <td>D</td> <td>C</td> </tr> </tbody> </table> <table border="1" data-bbox="448 1551 1295 1688"> <thead> <tr> <th>Adults</th> <th>Allogeneic HCT</th> <th>Autologous HCT</th> </tr> </thead> <tbody> <tr> <td>Germ cell tumor, relapse</td> <td>N</td> <td>S</td> </tr> <tr> <td>Germ cell tumor, refractory</td> <td>N</td> <td>S</td> </tr> </tbody> </table> <p><u>NCCN GUIDELINES™ Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (v.2.2023, June 2, 2023)</u> <u>Malignant Germ Cell Tumors</u> “High dose chemotherapy + stem cell transplant (SCT).” (category 2B) Footnote: “High-dose chemotherapy regimens vary among institutions.</p>	Children (<18 years)	Allogeneic HCT	Autologous HCT	Germ cell tumor, relapse	D	C	Germ cell tumor, refractory	D	C	Adults	Allogeneic HCT	Autologous HCT	Germ cell tumor, relapse	N	S	Germ cell tumor, refractory	N	S
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Cancer													
	<p>Some patients are potentially curable with stem cell transplantation. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for stem-cell transplant consultation and potentially curative therapy." (LCOC-13)</p> <p>"Patients achieving a complete clinical response after chemotherapy should be observed clinically every 2 to 4 months with AFP and beta-HCG levels (if initially elevated) for 2 years. For those with abnormal markers and definitive recurrent disease, options (category 2B) include: 1) high-dose chemotherapy; or 2) consider additional chemotherapy (see Principles of Systemic Therapy: Systemic Therapy Regimens – Malignant Germ Cell/Sex Cord-Stromal Tumors in the algorithm). Referral of these patients to a tertiary care center for stem-cell transplant consultation and potentially curative therapy is strongly recommended. Several case reports suggest that patients who have received chemotherapy for germ cell tumors may later present with growing teratoma syndrome." (MS-96)</p> <p><u>NCCN GUIDELINES™ Testicular Cancer (v.1.2023, January 26, 2023)</u> <u>Metastatic Germ Cell Tumors</u> "Second-line therapy options for patients with early relapses (within 2 years of the completion of primary therapy) include enrollment in a clinical trial (preferred), conventional-dose chemotherapy, or high-dose chemotherapy. If chemotherapy is given, both conventional-dose and high-dose regimens are preferred in this setting. The conventional-dose regimens are TIP or VeIP. The high-dose regimens include high-dose carboplatin plus etoposide followed by autologous stem cell transplant, or paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide with stem cell support." (MS-22)</p> <p><u>NCI Childhood Extracranial Germ Cell Tumors Treatment (PDQ®) February 10, 2023</u> <u>Nonstandard Treatment Options for Recurrent Malignant GCTs in Children</u> "The role of high-dose chemotherapy and hematopoietic stem cell rescue for recurrent pediatric GCTs is not established, despite anecdotal reports."</p>												
Kidney / Wilms tumor	<p><u>American Society for Transplantation and Cellular Therapy (2020)</u> (CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</p> <table border="1" data-bbox="448 1545 1295 1646"> <thead> <tr> <th data-bbox="448 1545 930 1612">Children (<18 years)</th> <th data-bbox="930 1545 1105 1612">Allogeneic HCT</th> <th data-bbox="1105 1545 1295 1612">Autologous HCT</th> </tr> </thead> <tbody> <tr> <td data-bbox="448 1612 930 1646">Wilms tumor, relapse</td> <td data-bbox="930 1612 1105 1646">N</td> <td data-bbox="1105 1612 1295 1646">C</td> </tr> </tbody> </table> <table border="1" data-bbox="448 1682 1295 1782"> <thead> <tr> <th data-bbox="448 1682 930 1749">Adults</th> <th data-bbox="930 1682 1105 1749">Allogeneic HCT</th> <th data-bbox="1105 1682 1295 1749">Autologous HCT</th> </tr> </thead> <tbody> <tr> <td data-bbox="448 1749 930 1782">Renal cancer, metastatic</td> <td data-bbox="930 1749 1105 1782">D</td> <td data-bbox="1105 1749 1295 1782">N</td> </tr> </tbody> </table> <p>No mention of stem cell transplant in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Kidney Cancer v.1.2024, June 21, 2023.</p>	Children (<18 years)	Allogeneic HCT	Autologous HCT	Wilms tumor, relapse	N	C	Adults	Allogeneic HCT	Autologous HCT	Renal cancer, metastatic	D	N
Children (<18 years)	Allogeneic HCT	Autologous HCT											
Wilms tumor, relapse	N	C											
Adults	Allogeneic HCT	Autologous HCT											
Renal cancer, metastatic	D	N											

Cancer							
	<p><u>NCI Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®) October 19, 2023</u></p> <p><u>Treatment of High-Risk and Very High-Risk Relapsed Wilms Tumor</u></p> <p>Treatment options for high-risk and very high-risk relapsed Wilms tumor include:</p> <ul style="list-style-type: none"> • “Chemotherapy, surgery, and/or radiation therapy. • Hematopoietic stem cell transplantation (HSCT): High-dose chemotherapy followed by autologous HSCT has been utilized for recurrent high-risk patients.” 						
Neuroblastoma	<p><u>American Society for Transplantation and Cellular Therapy (2020)</u></p> <p>(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</p> <table border="1" data-bbox="448 741 1295 873"> <thead> <tr> <th data-bbox="448 741 930 808">Children (<18 years)</th> <th data-bbox="930 741 1107 808">Allogeneic HCT</th> <th data-bbox="1107 741 1295 808">Autologous HCT</th> </tr> </thead> <tbody> <tr> <td data-bbox="448 808 930 873">Neuroblastoma, high risk or relapse</td> <td data-bbox="930 808 1107 873">D</td> <td data-bbox="1107 808 1295 873">S</td> </tr> </tbody> </table> <p><u>NCI Neuroblastoma Treatment (PDQ®) August 22, 2023</u></p> <p>“Generally, treatment is based on whether the tumor is low, intermediate, or high risk.”</p> <p>High risk: “For high-risk patients, treatment has intensified to include chemotherapy, surgery, radiation therapy, myeloablative therapy and stem cell transplant (SCT), isotretinoin, and immunotherapy, resulting in survival rates of 62%.”</p> <p>Treatment options for high-risk neuroblastoma typically include the following: “A regimen of chemotherapy, surgery, tandem cycles of myeloablative therapy and stem cell transplant (SCT), radiation therapy, and dinutuximab with granulocyte-macrophage colony-stimulating factor (GM-CSF) and isotretinoin.”</p> <p>“Treatment options for recurrent or refractory neuroblastoma in patients initially classified as high risk include the following:</p> <ol style="list-style-type: none"> 1. Chemotherapy combined with immunotherapy: <ol style="list-style-type: none"> a. Temozolomide, irinotecan, and dinutuximab. 2. 131I-MIBG. 131I-MIBG alone, in combination with other therapy, or followed by stem cell rescue. 3. Novel therapies: <ol style="list-style-type: none"> a. ALK inhibitors for patients with ALK mutations. b. WEE1 inhibitors 4. Chemotherapy (phase I/II studies): <ol style="list-style-type: none"> a. Topotecan in combination with cyclophosphamide or etoposide. b. Temozolomide with irinotecan. 5. Immunotherapy. Novel anti-GD2 drugs have been evaluated in patients with recurrent or refractory neuroblastoma. Hu14.18 anti-GD2 has been chemically linked with IL-2 and combined with GM- 	Children (<18 years)	Allogeneic HCT	Autologous HCT	Neuroblastoma, high risk or relapse	D	S
Children (<18 years)	Allogeneic HCT	Autologous HCT					
Neuroblastoma, high risk or relapse	D	S					

Cancer							
	<p>CSF, and a phase II trial of this regimen reported a few durable responses.</p> <p>Chemotherapy combined with immunotherapy produces the best response rate and response duration of treatments for high-risk patients with disease progression.”</p>						
Ovarian Epithelial	<p>NCCN GUIDELINES™ Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (v.2.2023, June 2, 2023) does not mention stem cell transplant for the treatment of epithelial ovarian cancer.</p> <p>No mention of stem cell transplant in National Cancer Institute (NCI) Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®) March 14, 2023.</p>						
Retinoblastoma	<p><u>NCI Retinoblastoma Treatment (PDQ®) April 11, 2023</u></p> <p>Treatment options for extraocular retinoblastoma (CNS disease) include the following:</p> <ul style="list-style-type: none"> • “Systemic chemotherapy and CNS-directed therapy with radiation therapy. • Systemic chemotherapy followed by myeloablative chemotherapy and stem cell rescue with or without radiation therapy.” <p>Extraocular retinoblastoma/Synchronous trilateral retinoblastoma treatment options include:</p> <ul style="list-style-type: none"> • “Systemic chemotherapy followed by surgery and myeloablative chemotherapy with stem cell rescue. • Systemic chemotherapy followed by surgery and radiation therapy.” <p>Extraocular retinoblastoma/Extracranial metastatic retinoblastoma treatment options include:</p> <ul style="list-style-type: none"> • “Systemic chemotherapy followed by myeloablative chemotherapy with stem cell rescue and radiation therapy.” <p>Extraocular retinoblastoma/Progressive or recurrent, treatment options include:</p> <ul style="list-style-type: none"> • “Systemic chemotherapy and radiation therapy for orbital disease. • Systemic chemotherapy followed by myeloablative chemotherapy with stem cell rescue and radiation therapy for extraorbital disease.” 						
Soft Tissue Sarcoma	<p><u>American Society for Transplantation and Cellular Therapy (2020)</u></p> <p>(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</p> <table border="1" data-bbox="448 1612 1295 1747"> <thead> <tr> <th data-bbox="448 1612 928 1682">Children (<18 years)</th> <th data-bbox="928 1612 1105 1682">Allogeneic HCT</th> <th data-bbox="1105 1612 1295 1682">Autologous HCT</th> </tr> </thead> <tbody> <tr> <td data-bbox="448 1682 928 1747">Soft tissue sarcoma, high risk or relapse</td> <td data-bbox="928 1682 1105 1747">D</td> <td data-bbox="1105 1682 1295 1747">D</td> </tr> </tbody> </table> <p>No mention of stem cell transplant in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Soft Tissue Sarcoma v.2.2022, May 17, 2022.</p>	Children (<18 years)	Allogeneic HCT	Autologous HCT	Soft tissue sarcoma, high risk or relapse	D	D
Children (<18 years)	Allogeneic HCT	Autologous HCT					
Soft tissue sarcoma, high risk or relapse	D	D					

Cancer	
	<p><u>NCI Childhood Rhabdomyosarcoma Treatment (PDQ®) January 10, 2023</u></p> <p><u>Other Therapeutic Approaches</u></p> <p>“High-dose chemotherapy with autologous and allogeneic stem cell rescue has been evaluated in a limited number of patients with rhabdomyosarcoma. The use of this modality has failed to improve the outcomes of patients with newly diagnosed or recurrent rhabdomyosarcoma.”</p>

Literature Review

Omazic et al. (2016) reported an analysis of data for 61 patients with solid cancer who underwent nonmyeloablative (n=23), reduced conditioning (n=36) or myeloablative (n=2) allogeneic HSCT. Two patients received cadaveric donor grafts. Types of solid cancers included in the study were metastatic renal carcinoma (n=22), cholangiocarcinoma (n=17), colon carcinoma (n=15), prostate cancer (n=3), pancreatic adenocarcinoma (n=3), or breast cancer (n=1). All patients with hepatic cholangiocarcinoma and one patient with colon carcinoma (with liver metastases) underwent orthotopic liver transplantation as debulking before HSCT. Three patients with pancreatic cancer underwent Whipple surgery with radical intent. Graft failure occurred in 13 patients (21%). The cumulative incidence of acute graft-versus-host disease (GVHD) of grades II to IV was 47%, and that of chronic GVHD was 32%. Treatment-related mortality at two years was 21%. Five-year cancer-related mortality was 63%; eight-year survival was 12%. Risk factors for mortality were nonmyeloablative conditioning (Hazard ratio [HR] 2.95; p < .001), absence of chronic GVHD (HR, 3.57; p < .001), acute GVHD of grades II to IV (HR, 2.90; p= .002), and HLA-identical transplant (HR, 5.00; p< 0.03). Five-year overall survival rates were 15% and 9% at 10 years. Data do not suggest an enduring benefit of allogeneic HSCT for the indications included in the study.

Central Nervous System: Peer-reviewed published data are limited to small prospective case series and retrospective reviews and support the use of autologous HSCT in the treatment of supratentorial primitive neuroectodermal tumor (PNET) and medulloblastoma (Sung 2013, Fangusaro 2008, Sung 2007).

Ewing Family of Tumors: The Ewing family of tumors is a group of cancers that start in the bones or nearby soft tissues that share some common features. These tumors can develop at any age, but they are most common in the early teen years. The main types of Ewing tumors are: 1) Ewing sarcoma of bone, 2) Extrasosseous Ewing tumor and 3) Peripheral primitive neuroectodermal tumor (PPNET). Several uncontrolled trials demonstrated improved or equivalent survival outcomes with autologous HSCT (Ferrari, 2011; Ladenstein, 2010).

Germ cell tumors: Several randomized controlled clinical trial data have not demonstrated improved health outcomes with the use of high-dose chemotherapy and autologous HSCT as a front-line therapy. Although data are not robust, the use of single or tandem HDC with autologous HSCT is considered an acceptable therapy for the treatment of individuals with refractory or relapsed testicular and ovarian germ cell tumors. For metastatic germ-cell tumors, three cycles of high-dose chemotherapy, each cycle followed by HSCT, is considered an appropriate second-line treatment option (Sharma, et al., 2020; Daugaard, 2011; Agawala, 2011; Lorch, 2011; Einhorn, 2007; Pico, 2005).

Neuroblastoma: Treatment of neuroblastoma is dependent on risk groups. The stage of neuroblastoma is one factor used to determine risk group. Other factors are the age of the child, tumor histology, and tumor biology. Autologous HSCT is a standard treatment option for

individuals classified as having high-risk disease. Improved survival has been demonstrated with the use of autologous HSCT compared with chemotherapy in several randomized controlled clinical trials. Although allogeneic HSCT has not been investigated in large numbers of patients, it may play a role in treatment of those patients who are not candidates for autologous HSCT when a HLA-matched donor is available (at least 5 of 6 HLA-match) (Berthold, et al., 2018; London, 2017; Yalcin, 2013; Ladenstein, 2008).

Retinoblastoma: Retinoblastoma is a relatively uncommon tumor of childhood that arises in the retina.

Several prospective case series and retrospective studies have suggested the safety and effectiveness of autologous HSCT for the treatment of retinoblastoma (Lee, 2008; Kremens, 2003). Treatment-related mortality was zero for all studies. In the study by Lee involving 14 children with bilateral disease, vision was preserved in one eye for nine patients and in both eyes for two patients; without the use of external beam radiation. Disease-free survival (DFS) ranged from 42–107 months (de Jong, 2014; Dunkel, 2010).

Soft tissue sarcoma: A retrospective analysis investigated the value of autologous stem cell transplantation (ASCT) according to histological subtype in soft-tissue sarcoma (STS) patients who were registered in the European Society for Blood and Marrow Transplantation database between 1996 and 2016. Median progression-free (PFS) and overall survival (OS) in the entire cohort of 338 patients were 8.3 and 19.8 months, respectively, and PFS and OS at 5 years were 13% and 25%, respectively. Analysis of outcomes in different subgroups showed that younger age, better remission status before transplantation and melphalan-based preparative regimen were predictive of benefit from ASCT, whereas histology and grading had no statistically significant impact. The authors noted that their data do not allow for conclusions as to whether specific histological subgroups benefit more from ASCT than others. Thus, the authors concluded, ASCT should not be performed in routine clinical practice (Heilig, et al., 2020).

Wilms tumor: Wilms tumor (also called Wilms’ tumor or nephroblastoma) is the most common type of kidney cancer in children. Results regarding benefit to event-free-survival (EFS) and overall survival (OS) are mixed; however, there are some data suggesting a survival benefit with high-dose chemotherapy and autologous HSCT for relapsed disease (Malogolowkin, 2017; Presson, 2010; Spreafico, 2008).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	STEM CELL Transplantation (Formerly 110.8.1) 110.23	1/27/2016
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information. (NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

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References

1. Agawala AK, Perkins SM, Abonour R, Brames MJ, Einhorn LH. Salvage chemotherapy with high-dose carboplatin and etoposide with peripheral blood stem cell transplant in patients with relapsed pure seminoma. *Am J Clin Oncol.* 2011 Jun;34(3):286-8.

2. American Cancer Society. Cancer Types. 2023. Accessed Nov 9, 2023. Available at URL address: <https://www.cancer.org/cancer/types.html>
3. Berthold F, Ernst A, Hero B, Klingebiel T, Kremens B, Schilling FH, Simon T. Long-term outcomes of the GPOH NB97 trial for children with high-risk neuroblastoma comparing high-dose chemotherapy with autologous stem cell transplantation and oral chemotherapy as consolidation. *Br J Cancer*. 2018 Aug;119(3):282-290.
4. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Nov 9, 2023, 2023. Available at URL address: <https://www.cms.gov/medicare-coverage-database/reports/local-coverage-proposed-lcds-alphabetical-report.aspx?proposedStatus=A&sortBy=title>
5. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Nov 9, 2023. Available at URL address: <https://www.cms.gov/medicare-coverage-database/reports/national-coverage-ncd-report.aspx?chapter=all&sortBy=title>
6. Daugaard G, Skoneczna I, Aass N, De Wit R, De Santis M, Dumez H, et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Gruppo Germinal (EORTC 30974). *Ann Oncol*. 2011 May;22(5):1054-61.
7. de Jong MC, Kors WA, de Graaf P, Castelijns JA, Kivelä T, et al. Trilateral retinoblastoma: a systematic review and meta-analysis. *Lancet Oncol*. 2014 Sep;15(10):1157-67.
8. Dunkel IJ, Khakoo Y, Kernan NA, Gershon T, Gilheeneey S. Intensive multimodality therapy for patients with stage 4a metastatic retinoblastoma. *Pediatr Blood Cancer*. 2010 Jul 15;55(1):55-9.
9. Einhorn HL, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med*. 2007 Jul 26;357(4):340-8.
10. Fangusaro J, Finlay J, Sposto R, Ji L, Saly M, Zacharoulis S, et al. Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors (sPNETs): report of the Head Start I and II experience. *Pediatr Blood Cancer*. 2008 Feb;50(2):312-8.
11. Ferrari S, Sundby Hall K, Luksch R, Tienghi A, Wiebe T, Fagioli F, et al. Nonmetastatic Ewing family tumors: high-dose chemotherapy with stem cell rescue in poor responder patients. Results of the Italian Sarcoma Group/Scandinavian Sarcoma Group III protocol. *Ann Oncol*. 2011 May;22(5):1221-7.
12. Frait E, Holuba MJ, Wray L. Pediatric Hematopoietic Stem Cell Transplant. *Pediatr Rev*. 2020 Nov;41(11):609-611.
13. Heilig CE, Badoglio M, Labopin M, Fröhling S, Secondino S, Heinz J, Nicolas-Virelizier E, Blaise D, Korenbaum C, Santoro A, Verbeek M, Krüger W, Siena S, Passweg JR, Di Nicola

M, Rifón J, Dreger P, Koehl U, Chabannon C, Pedrazzoli P; European Society for Blood and Marrow Transplantation (EBMT), Cellular Therapy & Immunobiology Working Party. Haematopoietic stem cell transplantation in adult soft-tissue sarcoma: an analysis from the European Society for Blood and Marrow Transplantation. *ESMO Open*. 2020 Oct;5(5):e000860.

14. Kanate AS, Majhail NS, Savani BN, Bredeson C, Champlin RE, Crawford S, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2020;26(7):1247-1256.
15. Kremens B, Wieland R, Reinhard H, Neubert D, Beck JD, et al. High-dose chemotherapy with autologous stem cell rescue in children with retinoblastoma. *Bone Marrow Transplant*. 2003 Feb;31(4):281-4.
16. Ladenstein R, Lasset C, Hartmann O, Klingebiel T, Bouffet E, Gadner R, et al. Comparison of auto versus allografting as consolidation of primary treatments in advanced neuroblastoma over one year of age at diagnosis: report from the European Group for Bone Marrow Transplantation. *Bone Marrow Transplant*. 1994 Jul;14(1):37-46.
17. Ladenstein R, Potschger U, Le Deley MC, Whelan J, Paulsson M, Oberlin O, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol*. 2010 Jul 10;28(20):3284-91.
18. Landry I. Racial disparities in hematopoietic stem cell transplant: a systematic review of the literature. *Stem Cell Investig*. 2021 Dec 14;8:24.
19. Lee SH, Yoo KH, Sung KW, Kim JY, Cho EJ, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with bilateral advanced retinoblastoma. *Bone Marrow Transplant*. 2008 Sep;42(6):385-91.
20. London WB, Bagatell R, Weigel BJ, Fox E, Guo D, et al. Historical time to disease progression and progression-free survival in patients with recurrent/refractory neuroblastoma treated in the modern era on Children's Oncology Group early-phase trials. *Cancer*. 2017 Dec 15;123(24):4914-4923.
21. Lorch A, Bascoul-Mollevis C, Kramar A, Einhorn L, Necchi A, Massard C, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. *J Clin Oncol*. 2011 Jun 1;29(16):2178-84.
22. Majhail NS, Nayyar S, Burton Santibañez ME, Murphy EA, Denzen EM. Racial disparities in hematopoietic cell transplantation in the United States. *Bone Marrow Transplant*. 2012 November ; 47(11).
23. Malogolowkin MH, Hemmer MT, Le-Rademacher J, Hale GA, Mehta PA, et al. Outcomes following autologous hematopoietic stem cell transplant for patients with relapsed Wilms tumor: a CIBMTR retrospective analysis. *Bone Marrow Transplant*. 2017 Nov;52(11):1549-1555.
24. National Cancer Institute (NCI). Cancer Types. Physician Data Query (PDQ®) Health Professional Version. Accessed Nov 9, 2023. Available at URL address: <https://www.cancer.gov/types>

25. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. Accessed Nov 10, 2023. Available at URL address: https://www.nccn.org/guidelines/category_1
26. National Marrow Donor Program. Diseases treatable by transplants. 2023. Accessed Nov 13, 2023. Available at URL address: <https://bethematch.org/transplant-basics/how-transplants-work/diseases-treatable-by-transplants/>
27. Omazic B, Remberger M, Barkholt L, Söderdahl G, Potáčová Z, Wersäll P, et al. Long-Term Follow-Up of Allogeneic Hematopoietic Stem Cell Transplantation for Solid Cancer. *Biol Blood Marrow Transplant*. 2016 Apr;22(4):676-681
28. Pico JL, Rosti G, Kramar A, Wandt H, Koza V, Salvioni R, et al. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. *Ann Oncol*. 2005 Jul;16(7):1152-9.
29. Presson A, Moore TB, Kempert P. Efficacy of high-dose chemotherapy and autologous stem-cell transplant for recurrent Wilms' tumor: a meta-analysis. *J Pediatr Hematol Oncol*. 2010 Aug;32(6):454-61.
30. Ratko TA, Belinson SE, Brown HM, Noorani HZ, Chopra RD, Marbella A, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population. Comparative Effectiveness Review No. 48. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. HHS 290-2007-10058.) AHRQ Publication No. 12-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2012. ARCHIVED. Accessed Nov 13, 2023. Available at URL address: <https://effectivehealthcare.ahrq.gov/topics/stem-cell-children/research>
31. Sharma A, Babra DS, Joshi PV, Hall M, Gogbashian A, et al. Survival Outcomes After High-dose Chemotherapy and Stem Cell Transplantation in the Salvage Setting for Relapsed or Refractory Germ Cell Cancers. *In Vivo*. 2020 Nov-Dec;34(6):3675-3679.
32. Spreafico F, Bisogno G, Collini P, Jenkner A, Gandola L, D'Angelo P, et al. Treatment of high-risk relapsed Wilms tumor with dose-intensive chemotherapy, marrow-ablative chemotherapy, and autologous hematopoietic stem cell support: experience by the Italian Association of Pediatric Hematology and Oncology. *Pediatr Blood Cancer*. 2008 Jul;51(1):23-8.
33. Sung KW, Lim DH, Son MH, Lee SH, Yoo KH, Koo HH et al. Reduced-dose craniospinal radiotherapy followed by tandem high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk medulloblastoma. *Neuro Oncol*. 2013 Mar;15(3):352-9.
34. Sung KW, Yoo KH, Cho EJ, Koo HH, Lim DH, Shin HJ, et al. High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor. *Pediatr Blood Cancer*. 2007 Apr;48(4):408-15.
35. Yalçın B, Kremer LCM, van Dalen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. *Cochrane Database of Systematic Reviews* 2015, Issue 10. Art. No.: CD006301.

Revision Details

Type of Revision	Summary of Changes	Date
Annual review	<ul style="list-style-type: none">Removed primary CNS lymphoma from the policy.	1/15/2024

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