Stem Cell Transplantation: Solid Tumors

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Related Coverage Resources

Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell (HPC) Boost
Stem Cell Transplantation: Blood Cancers
Transplantation Donor Charges
Umbilical Cord Blood Banking

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.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System (CNS) Tumors</td>
<td>All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.</td>
</tr>
<tr>
<td></td>
<td>Autologous HSCT is considered as medically necessary for the treatment of the following central nervous system tumors:</td>
</tr>
<tr>
<td></td>
<td>• supratentorial primitive neuroectodermal tumor (PNET)</td>
</tr>
<tr>
<td></td>
<td>• medulloblastoma</td>
</tr>
<tr>
<td></td>
<td>• relapsed or refractory primary CNS lymphoma.</td>
</tr>
<tr>
<td></td>
<td>Autologous HSCT is considered experimental, investigational or unproven for the treatment of ANY of the following central nervous system tumors:</td>
</tr>
<tr>
<td></td>
<td>• anaplastic glioma</td>
</tr>
<tr>
<td></td>
<td>• astrocytoma</td>
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<tr>
<td></td>
<td>• ependymoma</td>
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<tr>
<td></td>
<td>• glioblastoma</td>
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<td></td>
<td>• meningioma</td>
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<tr>
<td></td>
<td>• oligodendroglioma</td>
</tr>
<tr>
<td></td>
<td>• primary spinal cord tumors</td>
</tr>
<tr>
<td></td>
<td>Allogeneic HSCT is considered experimental, investigational or unproven for the treatment of central nervous system tumors.</td>
</tr>
<tr>
<td>Ewing Family of Tumors</td>
<td>Autologous HSCT is considered medically necessary for the treatment of relapsed or progressive Ewing family of tumors.</td>
</tr>
<tr>
<td>Germ Cell Tumors (e.g., testicular)</td>
<td>Single or tandem autologous HSCT is considered medically necessary for relapsed or refractory testicular and ovarian germ cell tumors.</td>
</tr>
<tr>
<td></td>
<td>Up to three autologous HSCT is considered medically necessary as second-line therapy for metastatic germ cell tumors.</td>
</tr>
<tr>
<td></td>
<td>EITHER of the following procedures for the treatment of testicular cancer is considered experimental, investigational or unproven:</td>
</tr>
<tr>
<td></td>
<td>• autologous HSCT as front-line therapy</td>
</tr>
<tr>
<td></td>
<td>• allogeneic HSCT</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Autologous HSCT is considered medically necessary for the treatment of high-risk neuroblastoma.</td>
</tr>
<tr>
<td></td>
<td>Allogeneic HSCT is considered medically necessary for the treatment of high-risk neuroblastoma when the individual is not a candidate for autologous HSCT.</td>
</tr>
<tr>
<td></td>
<td>A maximum of three tandem autologous HSCT is considered medically necessary for the treatment of high-risk neuroblastoma.</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Autologous HSCT is considered medically necessary for the treatment of retinoblastoma.</td>
</tr>
<tr>
<td>Wilms Tumor</td>
<td>Autologous HSCT is considered medically necessary for the treatment of relapsed Wilms tumor.</td>
</tr>
<tr>
<td>Adult - Other</td>
<td>HSCT for the treatment of ANY of the following solid tumors in an adult is considered experimental, investigational and unproven:</td>
</tr>
</tbody>
</table>
### Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria

All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.

- 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

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### 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 a "mini" or reduced intensity transplant, allows an individual to have less intensive chemotherapy before transplantation with allogeneic hematopoietic stem cells. This approach may be recommended for a
variety of reasons including age, type of disease, other medical issues, or prior therapies (UpToDate, 2018).

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 45%)
- 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)
- poor pulmonary function (diffusion capacity less than 60% of predicted)
- presence of human immunodeficiency virus or active hepatitis B, hepatitis C or human T-cell lymphotrophic 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 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, 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. For neuroblastoma, treatment depends 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.

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.

Professional Societies/Organizations
The table below includes information and recommendations from the following sources:

1. The American Society for Blood and Marrow Transplantation (ASBMT) Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation (Majhail, et al., 2015). The key to values within the table are as follows:
   - N indicates Not generally recommended
   - C: standard of care, clinical evidence available
   - S: standard of care
   - R: standard of care, rare indication
   - D: developmental
   - CR1: first complete response
   - CR2: second CR
   - CR3: third CR.

category 2A unless otherwise stated. If NCCN information is not included below, either there is no NCCN Clinical Practice Guideline or the applicable Clinical Practice Guideline does not address HSCT for that tumor/cancer type.


<table>
<thead>
<tr>
<th>Cancer</th>
<th>American Society for Blood and Marrow Transplantation (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (&lt;18 years)</td>
<td>Ewing's sarcoma, high risk or relapse: D</td>
<td>S</td>
</tr>
<tr>
<td>Adults</td>
<td>Ewing's sarcoma, high risk: N</td>
<td>C</td>
</tr>
</tbody>
</table>

**NCCN GUIDELINES™ Bone cancer (v.1.2020, August 12, 2019)**

**Ewing sarcoma**

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-16)

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-18)

**Osteosarcoma**

The safety and efficacy of HDT/SCT in patients with locally advanced, metastatic or relapsed osteosarcoma has been evaluated; however, efficacy in patients with high-risk disease is yet to be determined in prospective randomized studies. (MS-26,MS-27)

**NCI Ewing Sarcoma Treatment (PDQ®) August 15, 2019**

**High-Dose Chemotherapy With Stem Cell Support for Ewing Sarcoma**

For patients with a high risk of relapse with conventional treatments, certain investigators have utilized high-dose chemotherapy with hematopoietic stem cell transplant (HSCT) as consolidation treatment, in an effort to improve outcome.

**Standard Treatment Options for Localized Ewing Sarcoma**

An option includes high-dose chemotherapy and autologous stem cell rescue.

**Treatment of Metastatic Ewing Sarcoma**

More intensive therapies, many of which incorporate high-dose chemotherapy with or without total-body irradiation in conjunction with stem cell support, have not shown improvement in EFS rates for patients with bone and/or bone marrow metastases.

**Recurrent Ewing Sarcoma**
Cancer

| Treatment Options for Recurrent Osteosarcoma and MFH of Bone Treatment | Peripheral blood stem cell transplant utilizing high-dose chemotherapy does not appear to improve outcome. |
| Treatment Options for Recurrence With Bone-Only Metastases | Treatment options for patients with osteosarcoma or MFH of bone that has recurred in the bone only include: |
| • Surgery to remove the tumor. | 153Sm-EDTMP with or without stem cell support. |
| For patients with multiple unresectable bone lesions, 153Sm-EDTMP with or without stem cell support may produce stable disease and/or provide pain relief. |

### Breast Cancer

| American Society for Blood and Marrow Transplantation (2015) | (N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.) |
| Adults | Allogeneic HCT | Autologous HCT |
| Breast cancer, adjuvant high risk | N | D |
| Breast cancer, metastatic | D | D |

### Central Nervous System (CNS)

| American Society for Blood and Marrow Transplantation (2015) | (N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.) |
| Children (<18 years) | Allogeneic HCT | Autologous HCT |
| Medulloblastoma, high risk | N | C |
| Other malignant brain tumors | N | C |

### NCCN GUIDELINES™ Central Nervous System (CNS) cancers (v.3.2019, October 18, 2019)

#### Adult Medulloblastoma

Consider collecting stem cells before craniospinal radiation (AMED-2).

Treatment for Recurrence, High dose chemotherapy with autologous stem cell reinfusion.

Footnote: Only if the patient is without evidence of disease after surgery or conventional dose re-induction chemotherapy. (AMED-3)

#### Medulloblastoma and Supratentorial PNET

In the recurrence setting, high dose chemotherapy in combination with autologous stem cell transplantation is a feasible strategy for patients who have had good response with lower doses. (MS-15)
Cancer

<table>
<thead>
<tr>
<th>Medical Coverage Policy: 0534</th>
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<td>Medical Coverage Policy: 0534</td>
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<td>Medical Coverage Policy: 0534</td>
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</table>

**Cancer**

High dose chemotherapy with autologous stem cell rescue may be considered for patients showing no evidence of disease following resection or conventional reduction chemotherapy. (MS-16)

**Primary CNS Lymphoma**

- If complete response or complete response unconfirmed, consider high-dose chemotherapy with stem cell rescue (PCNS-2)
- Relapsed or refractory, consider high-dose therapy with stem cell rescue (Category 2B)
- Footnote: If the recurrent disease goes into complete remission with reduction chemotherapy. (PCNS-3)

High-dose chemotherapy with autologous stem cell transplantation in the relapsed or refractory setting has been tested with some success... although evidence of its advantage over conventional treatment is lacking. (MS-25)

**NCI Primary CNS Lymphoma Treatment (PDQ®) May 24, 2019**

**Consolidation After Induction Chemotherapy**

Several phase II studies have investigated consolidation with intensive chemotherapy supported by autologous stem cell transplantation (ASCT). This approach is most applicable for younger patients with few comorbidities and good performance status, who also respond well to induction therapy.

**NCI Childhood Astrocytoma’s Treatment (PDQ®) October 8, 2019**

Treatment options for recurrent childhood high-grade astrocytoma’s include:
- Surgery
- High-dose chemotherapy with stem cell transplant (SCT) (Not considered standard treatment)
- Targeted therapy with a BRAF inhibitor, for patients with a BRAF V600E mutation
- Early-phase clinical trial

**NCI Childhood Brain Stem Glioma Treatment (PDQ®) June 19, 2019**

Standard Treatment Options for Diffuse Intrinsic Pontine Gliomas (DIPGs)

Currently, no chemotherapeutic strategy—including neoadjuvant, concurrent, postradiation therapy, or immunotherapy—when added to radiation therapy has led to long-term survival for children with DIPGs. This includes studies utilizing high-dose, marrow-ablative chemotherapy with autologous hematopoietic stem cell rescue, which have also been ineffective in extending survival.

**NCI Childhood Medulloblastoma and Other Central Nervous System Embryonal Tumors Treatment (PDQ®) September 9, 2019**

**Treatment of Childhood Pineoblastoma, Treatment of children aged 3 years and younger**

- High-dose, marrow-ablative chemotherapy with autologous bone marrow rescue or peripheral stem cell rescue has been used with some success in young children.

**Treatment of Childhood Pineoblastoma, Treatment of children older than 3 years**

- Treatment options under clinical evaluation
For patients with pineoblastoma, a variety of different treatment approaches are under evaluation, including the use of higher doses of chemotherapy after radiation therapy supported by peripheral stem cell rescue and the use of chemotherapy during radiation therapy.

**Treatment of Recurrent Childhood Medulloblastoma and Other CNS Embryonal Tumors**

Treatment approaches may include High-dose chemotherapy with stem cell rescue. For patients who have previously received radiation therapy, higher-dose chemotherapeutic regimens, supported with autologous bone marrow rescue or peripheral stem cell support, have been used with variable results.

**NCI Childhood Central Nervous System Embryonal Tumors Treatment (PDQ®)**

**June 13, 2019**

**Treatment Options for Recurrent Childhood CNS GCTs**

Treatment options for recurrent childhood CNS GCTs include the following:

- Chemotherapy followed by additional radiation therapy.
- High-dose chemotherapy with stem cell rescue with or without additional radiation therapy

**NCI Childhood Ependymoma Treatment (PDQ®)**

**October 23, 2019**

**Treatment of Newly Diagnosed Childhood Ependymoma, Anaplastic Ependymoma, or RELA Fusion–Positive Ependymoma**

Treatment options for residual disease, no disseminated disease:

- There is no evidence that preirradiation high-dose chemotherapy with stem cell rescue is of any benefit.

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### Germ Cell Tumors

**American Society for Blood and Marrow Transplantation (2015)**

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th></th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
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</thead>
<tbody>
<tr>
<td><strong>Children (&lt;18 years)</strong></td>
<td></td>
<td></td>
</tr>
<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>
<thead>
<tr>
<th></th>
<th>Allogeneic HCT</th>
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<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germ cell tumor, relapse</td>
<td>N</td>
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<tr>
<td>Germ cell tumor, refractory</td>
<td>N</td>
<td>C</td>
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</tbody>
</table>

**NCCN GUIDELINES™ Ovarian cancers (v.2.2019, September 17, 2019)**

**Malignant Germ Cell Tumors**

High dose chemotherapy (Category 2B). Footnote: 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. (LCOH-12; OV-C, 8 of 10)
<table>
<thead>
<tr>
<th>Cancer</th>
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</thead>
<tbody>
<tr>
<td>For those with abnormal markers and definitive recurrent disease, options (2B category) include: high-dose chemotherapy or consider additional chemotherapy (see guidelines for Epithelial Ovarian cancer) Referral of these patients to a tertiary care center for SCT consultation and potentially curative therapy is strongly recommended. (MS-29)</td>
<td></td>
</tr>
<tr>
<td><strong>NCI Ovarian Germ Cell Tumors Treatment (PDQ®) February 12, 2016</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent Ovarian Germ Cell Tumors, Dysgerminomas</strong> Standard treatment options include cisplatin-based chemotherapy has been used effectively for patients with recurrent dysgerminoma with and without adjuvant radiation therapy.</td>
<td></td>
</tr>
<tr>
<td>Treatment options under ‘Clinical Evaluation’: Patients with recurrent pure dysgerminoma of the ovary are candidates for clinical trials. Some consideration should be given to the use of high-dose regimens with rescue.</td>
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<tr>
<td><strong>NCCN GUIDELINES™ Testicular Cancer (v.1.2020, October 9, 2019)</strong></td>
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<tr>
<td><strong>Metastatic Germ Cell Tumors</strong> Second line therapy options include high dose chemotherapy followed by autologous stem cell transplant. (MS-18, MS-19)</td>
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<tr>
<td><strong>NCI Testicular Cancer Treatment (PDQ®) February 6, 2019</strong></td>
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<tr>
<td><strong>Recurrent Testicular Cancer</strong> High-dose chemotherapy with autologous marrow transplantation has also been used in uncontrolled case series in the setting of recurrent disease. However, a randomized, controlled trial comparing conventional doses of salvage chemotherapy with high-dose chemotherapy with autologous marrow rescue showed more toxic effects and treatment-related deaths in the high-dose arm without any improvement in response rate or overall survival.</td>
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</tr>
<tr>
<td><strong>NCI Childhood Central Nervous System Germ Cell Tumors Treatment (PDQ®) June 13, 2019</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Treatment Options for Recurrent Childhood CNS germ cell tumors (GCTs) include:**  
  - Chemotherapy followed by additional radiation therapy.  
  - High-dose chemotherapy with stem cell rescue with or without additional radiation therapy.  
For pure germinoma patients who previously received radiation therapy, myeloablative chemotherapy with stem cell rescue has been used. High-dose chemotherapy and autologous stem cell rescue may also have curative potential for a minority of patients with relapsed systemic NGGCTs. |  |
| **NCI Childhood Extracranial Germ Cell Tumors Treatment (PDQ®) August 9, 2019** |  |
| **Nonstandard Treatment Options for Recurrent Malignant GCTs in Children** The role of high-dose chemotherapy and hematopoietic stem cell rescue for recurrent pediatric GCTs is not established, despite anecdotal reports. |  |
| **Kidney / Wilms tumor** |  |
| **American Society for Blood and Marrow Transplantation (2015)** (N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.) |  |
### Cancer

<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilms tumor, relapse</td>
<td>N</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults</th>
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<tbody>
<tr>
<td>Allogeneic HCT</td>
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<tr>
<td>----------------</td>
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<tr>
<td>Renal cancer, metastatic</td>
</tr>
</tbody>
</table>

**NCI Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®) June 13, 2019**

Treatment of High-Risk and Very High-Risk Relapsed Wilms Tumor

Treatment options for high-risk and very high-risk relapsed Wilms tumor include:
- Chemotherapy, surgery, and/or radiation therapy.
- Hematopoietic stem cell transplantation (HSCT).

The outcome of autologous stem cell rescue in selected patients is favorable; however, patients with gross residual disease going into transplant do not do as well. No randomized trials of chemotherapy versus transplant have been reported, and case series suffer from selection bias.

Patients in whom such salvage attempts fail should be offered treatment on available phase I or phase II studies.

### Neuroblastoma

**American Society for Blood and Marrow Transplantation (2015)**

<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma, high risk or relapse</td>
<td>D</td>
<td>S</td>
</tr>
</tbody>
</table>

**NCI Neuroblastoma Treatment (PDQ®) June 4, 2019**

The treatment of neuroblastoma has evolved over the past 60 years. Generally, treatment is based on whether the tumor is low, intermediate, or high risk.

**Treatment Options for High-Risk Neuroblastoma**

Outcomes for patients with high-risk neuroblastoma remain poor despite recent improvements in survival in randomized trials.

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 interleukin-2 (IL-2)/granulocyte-macrophage colony-stimulating factor (GM-CSF) and isotretinoin.

Treatment options for recurrent or refractory neuroblastoma in patients initially classified as high risk may include:
- 131I-MIBG alone, in combination with other therapy, or followed by stem cell rescue.
## Ovarian Epithelial

**Consolidation and/or maintenance therapy**

Phase III trials of consolidation and/or maintenance therapy have been carried out with cytotoxic drugs that contribute to the treatment of recurrent ovarian cancer, vaccines, and radioimmunoconjugates listed below with mostly negative results:

- High-dose chemotherapy with hematopoietic support

## Retinoblastoma

**NCI Retinoblastoma Treatment (PDQ®) November 7, 2019**

Extraocular retinoblastoma/CNS disease treatment options include:

- Systemic chemotherapy and CNS-directed therapy.
- Systemic chemotherapy followed by myeloablative chemotherapy and stem cell rescue.

Extraocular retinoblastoma/Synchronous trilateral retinoblastoma treatment options include:

- Systemic chemotherapy followed by surgery and myeloablative chemotherapy with stem cell rescue.
- Systemic chemotherapy followed by surgery and radiation therapy.

Extraocular retinoblastoma/Extracranial metastatic retinoblastoma treatment options include:

- Systemic chemotherapy followed by myeloablative chemotherapy with stem cell rescue and radiation therapy.

Extraocular retinoblastoma/Progressive or recurrent, treatment options include:

- 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

**American Society for Blood and Marrow Transplantation (2015)**

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue sarcoma, high risk or relapse</td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>

**NCI Childhood Rhabdomyosarcoma Treatment (PDQ®) August 21, 2019**

**Other Therapeutic Approaches**

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.

**NCI Childhood Soft Tissue Sarcoma Treatment (PDQ®) August 16, 2019**

**Desmoplastic small round cell tumor**

There is no standard approach to the treatment of desmoplastic small round cell tumor.
The Center for International Blood and Marrow Transplant Research (CIBMTR) analyzed patients with desmoplastic small round cell tumor in their registry who received consolidation with high dose chemotherapy and autologous stem cell reconstitution. While this retrospective registry analysis suggested some benefit for this approach, other investigators have abandoned the approach because of excessive toxicity and lack of efficacy.


NCCN GUIDELINES™ Gestational Trophoblastic Neoplasia (v.2.2019, May 6, 2019)
Gestational Trophoblastic Neoplasia (GTN)
Additional regimes shown to have some activity in treating resistant GTN: High dose chemotherapy with peripheral stem cell transplantation (GTN-A, 4 of 5 and 5 of 5)

NCI Childhood Liver Cancer Treatment (PDQ®) October 8, 2019
Treatment options for hepatoblastoma with metastases at diagnosis
- High-dose chemotherapy with stem cell rescue does not appear to be more effective than standard multiagent chemotherapy

NCI Langerhans Cell Histiocytosis Treatment (PDQ®) June 13, 2019
Treatment of High-Risk Multisystem LCH
Treatment options for patients with recurrent, refractory, or progressive high-risk multisystem disease include:
- Chemotherapy.
- Hematopoietic stem cell transplantation (HSCT).

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) as well as primary CNS lymphoma (DeFilipp, 2017; Omuro, 2015; Kasenda, 2012; Montemurro, 2007; Colombat, 2006; Soussain, 2001).

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) Extraosseous 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 (Daugaard, 2011; Agawala, 2011; Lorch, 2011; Einhorn, 2007; Pico, 2005).

**Neuroblastoma:** For neuroblastoma, treatment depends 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) (London, 2017; Yalcin, 2015; 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 on two patients; without the use of external beam radiation. Disease-free survival (DFS) ranged from 42–107 months (de Jong, 2014; Dunkel, 2010).

**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).

**American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative**

No relevant statements.

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCDs): STEM CELL Transplantation (Formerly 110.8.1) (110.23), last revised 1/27/2016. Coverage Policy is broader in scope than NCD. Refer to the CMS NCD table of contents link in the reference section.
- Local Coverage Determinations (LCDs): No LCDs found.

**Use Outside of the US**

The European Society for Medical Oncology has published numerous Clinical Practice Guidelines related to various solid tumors cancers.

### Coding/Billing Information

**Note:**

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:**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
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**Medical Coverage Policy: 0534**

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<th>Code</th>
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<td>38206</td>
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<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
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<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
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<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
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<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
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<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
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<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
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<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
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<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
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<td>Bone marrow harvesting for transplantation; allogeneic</td>
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<td>Bone marrow harvesting for transplantation; autologous</td>
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<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
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**HCPCS Codes**

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<td>S2142</td>
<td>Cord blood derived stem-cell transplantation, allogeneic</td>
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<tr>
<td>S2150</td>
<td>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</td>
</tr>
</tbody>
</table>


**References**


