Medical Policy
Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood

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Policy Number: 208
BCBSA Reference Number: 8.01.34
NCD/LCD: National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1)

Related Policies
Hematopoietic Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma, #205

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Autologous hematopoietic stem-cell transplantation for solid tumors of childhood may be **MEDICALLY NECESSARY** for the following conditions:
- Initial treatment of high-risk neuroblastoma,
- Recurrent or refractory neuroblastoma,
- Initial treatment of high-risk Ewing’s sarcoma, and
- Recurrent or refractory Ewing’s sarcoma.

Tandem autologous hematopoietic stem-cell transplantation may be **MEDICALLY NECESSARY** for high-risk neuroblastoma.

Autologous hematopoietic stem-cell transplantation for solid tumors of childhood is **INVESTIGATIONAL** for the following conditions:
- Initial treatment of low- or intermediate-risk neuroblastoma,
- Initial treatment of low- or intermediate-risk Ewing’s sarcoma, Initial treatment of other solid tumors of childhood including, but not limited, to the following:
  - Rhabdomyosarcoma,
  - Wilms tumor,
  - Osteosarcoma
  - Retinoblastoma.
Tandem autologous hematopoietic stem-cell transplantation for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma, as noted above is INVESTIGATIONAL.

Allogeneic (myeloablative or nonmyeloablative) hematopoietic stem-cell transplantation for treatment of pediatric solid tumors is INVESTIGATIONAL.

Salvage allogeneic (myeloablative or nonmyeloablative) hematopoietic stem-cell transplantation for treatment of neuroblastoma or pediatric solid tumors is INVESTIGATIONAL in the following conditions:

- Relapse after autologous transplant
- Failure of tumor after autologous transplant.

National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1)

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD-9 Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; autologous</td>
</tr>
<tr>
<td>38243</td>
<td>Hematopoietic progenitor cell (HPC); HPC boost</td>
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<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation,</td>
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allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

### ICD-9 Procedure Codes

<table>
<thead>
<tr>
<th>ICD-9-CM procedure codes:</th>
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<tr>
<td>41.00</td>
<td>Bone marrow transplant, not otherwise specified</td>
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<tr>
<td>41.01</td>
<td>Autologous bone marrow transplant without purging</td>
</tr>
<tr>
<td>41.04</td>
<td>Autologous hematopoietic stem cell transplant without purging</td>
</tr>
<tr>
<td>41.06</td>
<td>Cord blood stem cell transplant</td>
</tr>
<tr>
<td>41.07</td>
<td>Autologous hematopoietic stem cell transplant with purging</td>
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<td>41.09</td>
<td>Autologous bone marrow transplant with purging</td>
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### ICD-10 Procedure Codes

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<tr>
<td>30233G0</td>
<td>Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233X0</td>
<td>Transfusion of Autologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243G0</td>
<td>Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243X0</td>
<td>Transfusion of Autologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30263G0</td>
<td>Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach</td>
</tr>
<tr>
<td>30263X0</td>
<td>Transfusion of Autologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach</td>
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<tr>
<td>30263Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach</td>
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<tr>
<td>3E03305</td>
<td>Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach</td>
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<td>3E04305</td>
<td>Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach</td>
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<tr>
<td>3E05305</td>
<td>Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach</td>
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<tr>
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<td>Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach</td>
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The following CPT, HCPCS and ICD Procedure codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
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<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
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</tbody>
</table>
Description

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. Autologous HSCT takes advantage of the steep dose-response relationship observed with many chemotherapeutic agents and
allows for escalation of chemotherapy doses above those limited by myeloablation. The use of allogeneic HSCT for solid tumors relies on a graft-versus-tumor effect; however, allogeneic HSCT is rarely used in childhood solid tumors.

**Solid Tumors of Childhood**

Solid tumors of childhood are defined as masses or multiple masses within the body, which do not originate from myeloid or lymphoid cells within the bone marrow. (Liquid tumors of childhood, contrastingly, do originate from myeloid or lymphoid cells within the bone marrow and circulate within the blood stream.) Some of the most common solid tumors of childhood are neuroblastoma, Ewing’s sarcoma/Ewing’s Sarcoma Family of Tumors, Wilms tumor, rhabdomyosarcoma, osteosarcoma, and retinoblastoma.

The prognosis for pediatric solid tumors has improved over the last two decades, mostly due to the application of multiagent chemotherapy and improvements in local control therapy (including aggressive surgery and advancements in radiation therapy). However, patients with metastatic, refractory, or recurrent disease continue to have poor prognoses, and these “high-risk” patients are candidates for more aggressive therapy, including autologous hematopoietic stem-cell transplantation (HSCT), in an effort to improve event-free survival and overall survival.

Brief descriptions of the solid tumors of childhood that are addressed in this policy are as follows.

**Peripheral Neuroblastoma**

Neuroblastoma is the most common extracranial solid tumor of childhood, with two-thirds of the cases presenting in children younger than 5 years of age. They are remarkable for their broad spectrum of clinical behavior, with some undergoing spontaneous regression, others differentiating into benign tumors, and still others progressing rapidly and resulting in patient death. These tumors originate where sympathetic nervous system tissue is present.

In general, most patients with low-stage disease have excellent outcomes with minimal therapy, and many patients with localized tumors without lymph node involvement can be treated by surgery alone. Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery. In contrast, most children older than 1 year with advanced-stage disease die due to progressive disease, despite intensive multimodality therapy. Treatment of recurrent disease is determined by the risk group at the time of diagnosis, and the extent of disease and age of the patient at recurrence.

**Ewing’s Sarcoma and the Ewing Family of Tumors**

Ewing’s sarcoma family of tumors (ESFT) encompasses a group of tumors that have in common some degree of neural/glial differentiation and a characteristic underlying molecular pathogenesis (chromosomal translocation which function as oncogenic transcription factors). Included in ESFT are “classic” Ewing’s sarcoma of bone, extraosseous Ewing’s, peripheral primitive neuroectodermal tumor, and Askin tumors.

Most commonly diagnosed in adolescence, ESFT can be found in bone or soft tissue; however, the spectrum of ESFT has also been described in various organ systems. Ewing’s is the second most common primary malignant bone tumor with most common sites occurring in the pelvis long bones of the lower extremities, and the bones of the chest wall.

Multiagent chemotherapy, surgery, and radiation therapy have improved the progression free survival (PFS) in patients with localized disease to 60%–70%. The presence of metastatic disease is the most unfavorable prognostic feature, and the outcome for patients presenting with metastatic disease is poor, with 20%–30% PFS. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing’s are tumor location, larger tumor size, and older age of the patient. Thirty to forty percent of patients with ESFT experience disease recurrence and patients with recurrent disease have a 5-year event free survival and overall survival rate of less than 10%.

**Rhabdomyosarcoma**

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. Most frequently occurring primary sites are the head and neck (e.g., parameningeal, orbital, pharyngeal), genitourinary
tract, and extremities. Most children with RMS present with localized disease, and with conventional multimodal therapy, the cure rate in this group is 70%–80%. However, approximately 15% of children present with metastatic disease, and despite the introduction of new drugs and intensified treatment, the 5-year survival is 20%–30% for this “high-risk” group.

**Wilms Tumor**
Wilms tumor, the most common primary malignant renal tumor of childhood, is highly sensitive to chemotherapy and radiation, and current cure rates exceed 85%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse less than 6–12 months after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases) event-free survival is less than 15%. However, recent clinical trials (although data are not robust) suggest that high-dose chemotherapy with autologous HSCT offers improved survival over standard treatment in selected patients increasing the overall survival rates to 60-73%.

**Osteosarcoma**
Osteosarcoma is a primary malignant bone tumor that is characterized by formation of bone or osteoid by the tumor cells. More than 50% of these tumors arise from bones around the knee. The prognosis of localized osteosarcoma has greatly improved over the last 30 years with OS rates increasing from 10% with surgery alone (usually amputation) to 70% with the introduction of neoadjuvant chemotherapy and limb-sparing surgery. However, 30%–40% of patients with non-metastatic osteosarcoma of the extremities experience recurrent disease, most commonly in the lungs and exhibit a mean 5-year post-relapse survival rate of approximately 28%, with some groups having a 0% rate. Prognostic factors for recurrence include site and size of the primary tumor, presence of metastases at the time of diagnosis, resection adequacy, and tumor response to preoperative chemotherapy (measured as percent of tumor necrosis in the resection specimen). Overall event free survival for patients with metastatic disease at diagnosis is about 20%–30%.

**Retinoblastoma**
Retinoblastoma is the most common primary tumor of the eye in children. Retinoblastoma is usually confined to the eye, and with current therapy has at least a 90% cure rate. However, once disease has spread beyond the eye, survival rates drop significantly; 5-year disease-free survival is reported to be less than 10%.

**Summary**

**Neuroblastoma**
The use of single autologous HSCT has become a widely accepted treatment option for children with high-risk neuroblastoma, after randomized studies have shown improved EFS and OS.

No studies directly comparing single autologous to tandem autologous HSCT for high-risk neuroblastoma have been published; however, case series on the use of tandem autologous for high-risk neuroblastoma have reported EFS rates superior to those reported with the use of single autologous HSCT (reported in randomized trials comparing single autologous HSCT to conventional chemotherapy).

Some transplant centers use tandem autologous HSCT as the preferred approach to the treatment of high-risk neuroblastoma.

A Phase III, randomized trial of single versus tandem autologous HSCT for high-risk neuroblastoma is currently underway.

**Ewing’s sarcoma family of tumors (ESFT)**
Data for the use of HSCT in the initial treatment of high-risk or recurrent or refractory ESFT have shown varied results for a survival benefit with the use of HSCT. Two Phase III trials are currently underway using risk-stratified approaches, which will likely serve to guide future treatment options for ESFT.

**Rhabdomyosarcoma**
The use of HSCT for metastatic rhabdomyosarcoma (RMS) has failed to show a survival benefit.
**Wilms tumor**
The use of HSCT for high-risk relapsed Wilms tumor, in general, has failed to show a survival benefit, although a few reports have suggested some benefit in certain subpopulations (e.g., patients with advanced-stage disease with lung-only metastases). A Phase II trial is currently underway using a risk-stratified approach to treatment and includes high-risk patients who will be treated with HSCT.

**Osteosarcoma**
The use of HSCT for osteosarcoma has failed to show a survival benefit.

**Retinoblastoma**
Small case series and case reports have shown prolonged DFS in some patients with stage 4 disease treated with HSCT, particularly those with stage 4a disease.

A recent study (47) of 15 patients showed that some patients with stage 4a retinoblastoma were cured with the use of HSCT. A prospective multicenter trial (COG ARET 0321) is underway to better determine the role of HSCT in patients with retinoblastoma.

**Allogeneic HSCT**
Studies using allogeneic HSCT for pediatric solid tumors, either upfront or as salvage therapy after a failed autologous HSCT are lacking. A large retrospective review of the use of allogeneic HSCT for high-risk neuroblastoma (24) failed to show a survival benefit over autologous HSCT and was associated with a higher risk of transplant-related mortality.

### Policy History

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<td>1/2015</td>
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<tr>
<td>12/2012</td>
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References


