Introduction

The bone marrow is filled with cells known as hematopoietic stem cells. These immature cells develop into different types of blood cells: white blood cells to fight infection, red blood cells to carry oxygen, and platelets to clot the blood. In some cases, treating cancer also means destroying the bone marrow’s natural ability to create healthy blood cells. Restoring this function means returning these immature cells — the hematopoietic stem cells — to the body. When the immature blood cells come from a donor it’s known as an allogeneic transplant. When the cells are collected from the patient, stored, and later given back to the same patient it’s called an autologous transplant (autologous means from the same person). This policy describes when these transplants may be considered medically necessary for specific types of solid tumors that usually develop during childhood.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous hematopoietic cell transplantation</strong></td>
<td>Autologous hematopoietic cell transplantation may be considered medically necessary for:</td>
</tr>
<tr>
<td></td>
<td>• Initial treatment of high-risk neuroblastoma</td>
</tr>
<tr>
<td></td>
<td>• Recurrent or refractory neuroblastoma</td>
</tr>
<tr>
<td></td>
<td>• Initial treatment of high-risk Ewing’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>• Recurrent or refractory Ewing’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>• Metastatic Retinoblastoma</td>
</tr>
<tr>
<td><strong>Tandem autologous hematopoietic cell transplantation</strong></td>
<td>Tandem autologous hematopoietic cell transplantation is considered medically necessary for high-risk, refractory or relapsed neuroblastoma.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous hematopoietic cell transplantation</strong></td>
<td>Autologous hematopoietic cell transplantation is considered investigational as initial treatment of low- or intermediate-risk neuroblastoma, initial treatment of low- or intermediate-risk Ewing’s sarcoma, and for other solid tumors of childhood including, but not limited, to the following:</td>
</tr>
<tr>
<td></td>
<td>• Rhabdomyosarcoma</td>
</tr>
<tr>
<td></td>
<td>• Osteosarcoma</td>
</tr>
<tr>
<td></td>
<td>• Wilms Tumors</td>
</tr>
<tr>
<td><strong>High-dose chemotherapy autologous cell support</strong></td>
<td>High-dose chemotherapy (with or without associated radiotherapy) and autologous cell support may be considered investigational for treatment of recurrent Wilms tumor</td>
</tr>
<tr>
<td><strong>Tandem autologous hematopoietic cell transplantation</strong></td>
<td>Tandem autologous hematopoietic cell transplantation is considered investigational for treatment of all other types of pediatric solid tumors.</td>
</tr>
<tr>
<td><strong>Allogeneic hematopoietic cell transplantation</strong></td>
<td>Allogeneic (myeloablative or nonmyeloablative) hematopoietic cell transplantation is considered investigational for treatment of pediatric solid tumors.</td>
</tr>
<tr>
<td><strong>Salvage allogeneic hematopoietic cell transplantation</strong></td>
<td>Salvage allogeneic hematopoietic cell transplantation for pediatric solid tumors that relapse after autologous transplant or fail to respond is considered investigational.</td>
</tr>
</tbody>
</table>
**Documentation Requirements**

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

**For autologous hematopoietic cell transplantation**

Office visit notes that contain the relevant history and physical supporting any of the following situations:

- As the first treatment of high-risk neuroblastoma
- For neuroblastoma that didn’t respond to treatment or that came back
- As the first treatment for high-risk Ewing’s sarcoma
- For Ewing’s sarcoma that didn’t respond to treatment or came back
- Retinoblastoma that has spread to other parts of the body

**For tandem autologous hematopoietic cell transplantation**

- Office visit notes that contain the relevant history and physical supporting that patient has childhood neuroblastoma that is high risk, doesn’t respond to treatment, or has returned.

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**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
<tr>
<td><strong>HCPCS</strong></td>
<td></td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: phoresis 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</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td></td>
<td>definition</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information

This policy addresses peripheral neuroblastoma, those arising from the peripheral nervous system.

### Definition of Terms

**Hematopoietic cell transplantation (HCT):** This refers to any source of stem cells, i.e., autologous, allogeneic, syngeneic, or umbilical cord blood.

**Primary refractory disease:** This is defined as a tumor that does not achieve a complete remission after initial standard-dose chemotherapy.

**Relapse:** This is defined as tumor recurrence after a prior complete response.

**RIC:** This refers to reduced intensity conditioning.

**Salvage transplantation:** This is defined as a hematologic cell transplantation (HCT), either autologous, allogeneic, or RIC-allogeneic. It is used as a second-line therapy after failure of primary therapy of any type. Salvage transplantation is sometimes referred to as a “rescue” transplant. It implies that the original therapy has failed. A salvage second HCT is often an autologous HCT if the prior therapy is chemotherapy. If the prior therapy is a failed autologous transplant a salvage second HCT would more likely be an allogeneic HCT or an RIC-allogeneic HCT. Typically, a salvage transplantation is done after enough time has elapsed to identify that the primary therapy has failed, so the interval between the two transplants would be longer.

**Tandem transplantation:** This is defined as a HCT technique where the preplanned intent for therapy involves two sequential HCTs. These may be autologous followed by a second autologous (auto-auto) transplantation, autologous followed by allogeneic (auto- allo) transplantation, or autologous followed by RIC-allogeneic (auto–RIC- allo) transplantation. The
“tandem” implies a very short preplanned interval between the two transplants, as well as the therapeutic intent to do two transplants from the outset of therapy.

**Benefit Application**

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).

- Some contracts or certificates of coverage may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

**Evidence Review**

**Description**

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs, with or without whole body radiotherapy. Stem cells may be obtained from the transplant recipient (autologous HCT) or harvested from a donor (allogeneic HCT). Stem cells may be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

**Background**

**Solid Tumors of Childhood**

Solid tumors of childhood arise from mesodermal, ectodermal, and endodermal cells of origin. Some common solid tumors of childhood are neuroblastoma, Ewing's sarcoma/Ewing's sarcoma family of tumors (ESFT), Wilms tumor, rhabdomyosarcoma (RMS), osteosarcoma, and retinoblastoma.
General Treatment

The prognosis for pediatric solid tumors has improved more recently, 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 cell transplantation (HCT), to improve event-free survival and overall survival.

Descriptions of pediatric-onset solid tumors addressed herein are as follows.

Peripheral Neuroblastoma

Neuroblastoma is the most common extra cranial solid tumor of childhood, with approximately 90% of the cases presenting in children younger than 5 years of age. These tumors originate where sympathetic nervous system tissue is present, within the adrenal medulla or paraspinal sympathetic ganglia, but have diverse clinical behavior depending on a variety of risk factors.

Patients with neuroblastoma are stratified into prognostic risk groups (low, intermediate, and high) that determine treatment plans. Risk variables include age at diagnosis, clinical stage of disease, tumor histology, and certain molecular characteristics, including the presence of the MYCN oncogene. Tumor histology is categorized as favorable or unfavorable, according to the degree of tumor differentiation, the proportion of tumor stromal component, and index of cellular proliferation. It is well established that MYCN amplification is associated with rapid tumor progression and a poor prognosis, even in the setting of other coexisting favorable factors. Loss of heterozygosity (LOH) at chromosome arms 1p and 11q occurs frequently in neuroblastoma. Although 1p LOH is associated with MYCN amplification, 11q is usually found in tumors without this abnormality. Some studies have shown that 1p LOH and unbalanced 11q LOH are strongly associated with outcome in patients with neuroblastoma, and both are independently predictive of worse progression-free survival (PFS) in patients with low- and intermediate-risk disease. Although the use of these LOH markers in assigning treatment in patients is evolving, they may prove useful to stratify treatment.

In the early 1990s, a uniform clinical staging system based on surgical resectability and distant spread, the International Neuroblastoma Staging System, was adopted by pediatric cooperative groups as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localized tumor with complete gross excision, with or without microscopic residual disease; lymph nodes</td>
</tr>
<tr>
<td>Stage</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross excision; lymph nodes negative for tumor</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration or by lymph node involvement</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (marrow involvement less than 10%), limited to children younger than 1 year of age</td>
</tr>
</tbody>
</table>

The low-risk group includes patients younger than one year of age with stage 1, 2, or 4S with favorable histopathologic findings and no MYCN oncogene amplification. High-risk neuroblastoma is characterized by an age older than 1 year, disseminated disease, MYCN oncogene amplification, and unfavorable histopathologic findings.

The International Neuroblastoma Risk Group (2009) proposed a revised staging system, which incorporated pretreatment imaging parameters instead of surgical findings as follows.\(^7\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Localized tumor not involving vital structures as defined by the list of Image-Defined Risk Factors and confined to one body compartment</td>
</tr>
<tr>
<td>L2</td>
<td>Locoregional tumor with presence of one or more Image-Defined Risk Factors</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastatic disease (except stage MS)</td>
</tr>
<tr>
<td>MS</td>
<td>Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow</td>
</tr>
</tbody>
</table>

**Treatment**

In general, most patients with low-stage disease have excellent outcomes with minimal therapy, and with International Neuroblastoma Staging System stage 1 disease, most patients can be treated by surgery alone.\(^8\) Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.\(^8\) In contrast, most children older than 1 year with advanced-stage disease die due to progressive disease, despite intensive multimodality therapy,\(^8\) and relapse remains common. 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.
For intermediate-risk disease, moderately intensive multiagent chemotherapy is the mainstay of therapy.\(^9\) Surgery is needed to obtain a diagnosis, and the extent of resection necessary to obtain an optimal outcome is not established.\(^10\) Patients at high-risk have historically had very low (<15%) long-term overall survival. Current therapy for high-risk disease typically includes an aggressive multimodal approach with chemotherapy, surgical resection, and radiotherapy.\(^11\)

Treatment of recurrent disease is determined by the risk group at diagnosis and the extent of disease and age of the patient at recurrence.

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

ESFT encompasses a group of tumors that share some degree of neuroglial differentiation and a characteristic underlying molecular pathogenesis (chromosomal translocation). The translocation usually involves chromosome 22 and results in fusion of the EWS gene with one of the members of the ETS family of transcription factors, either FLI1 (90–95%) or ERG (5–10%). These fusion products function as oncogenic aberrant transcription factors. Detection of these fusions is considered to be specific for the ESFT and helps further validate the diagnosis. Included in ESFT are “classic” Ewing’s sarcoma of bone, extra-osseous Ewing’s, peripheral primitive neuroectodermal tumor (pPNET), and Askin tumors (chest wall).

Most commonly diagnosed in adolescence, ESFT can be found in bone (most commonly) 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. The most common primary sites are the pelvic bones, the long bones of the lower extremities, and the bones of the chest wall.

**Treatment**

Current therapy for Ewing’s sarcoma typically includes induction chemotherapy, followed by local control with surgery and/or radiotherapy (dependent on tumor size and location), followed by adjuvant chemotherapy. Multiagent chemotherapy, surgery, and radiotherapy have improved the progression-free survival rates in patients with localized disease to 60–70%.\(^12\) 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% progression-free survival. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing’s are tumor location (eg, patients with pelvic primaries have worse outcomes), larger tumor size, and older age of the patient. However, “high-risk” Ewing’s has not always been consistently defined in the literature.
Rhabdomyosarcoma

Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma of childhood, shows skeletal muscle differentiation. The most common primary sites are the head and neck (eg, parameningeal, orbital, pharyngeal), genitourinary tract, and extremities.\textsuperscript{13}

**Treatment**

Specific treatment is based on tumor location, resection, and node status, and may involve surgery, radiotherapy, and chemotherapy.\textsuperscript{14} Five-year survival rates for rhabdomyosarcoma increased between 1975 and 2010 from 53% to 67% in children younger than 15 years and from 30% to 51% in 15- to 19-year-olds.\textsuperscript{13}

Approximately 15% of children present with metastatic disease, and despite the introduction of new drugs and intensified treatment, the 5-year survival is 20% to 30% for this “high-risk” group.\textsuperscript{15,16} Similarly, post-relapse mortality is very high. The prognosis of metastatic disease is affected by tumor histology, age at diagnosis, the site of metastatic disease, and the number of metastatic sites.\textsuperscript{13}

Wilms Tumor

Wilms tumor is the most common primary malignant renal tumor of childhood. In the United States, Wilms tumor is staged using the National Wilms Tumor Study system, which is based on surgical evaluation before chemotherapy as shown below.\textsuperscript{17}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| I     | (a) Tumor is limited to the kidney and completely excised;  
(b) The tumor was not ruptured before or during removal;  
(c) The vessels of the renal sinus are not involved beyond 2 mm  
(d) There is no residual tumor apparent beyond the margins of excision |
| II    | (a) Tumor extends beyond the kidney but is completely excised  
(b) No residual tumor is apparent at or beyond the margins of excision  
(c) Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor |
<p>| III   | Residual tumor confined to the abdomen: |</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Presence of hematogenous metastases or metastases to distant lymph nodes</td>
</tr>
<tr>
<td>V</td>
<td>Bilateral renal involvement at the time of initial diagnosis</td>
</tr>
</tbody>
</table>

Adapted from Metzger and Dome (2005).

**Treatment**

In the United States, National Wilms Tumor Study and Children’s Oncology Group protocols are based on primary resection for unilateral tumors, followed by escalating levels of chemotherapy and radiotherapy depending on tumor stage and other prognostic factors. Tumor histology, tumor stage, molecular and genetic markers (eg, LOH at chromosome 16q), and age (>2 years) are all associated with increased risks of recurrence and death. Wilms tumors are highly sensitive to chemotherapy and radiotherapy, and current cure rates exceed 85%. Between 10% and 15% of patients with favorable histology and 50% of patients with anaplastic tumors, experience tumor progression or relapse.

Similar risk-adapted strategies are being tested for the 15% of patients who experience a relapse. Success rates after relapse range from 25% to 45%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse <6 to 12 months after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases), the event-free survival rate is less than 15%.

**Osteosarcoma**

Osteosarcoma is a primary malignant bone tumor and the most common bone cancer in children and adolescents; it is characterized by infiltration of bone or osteoid by the tumor cells. Peak incidence occurs around puberty, most commonly in long bones such as the femur or humerus. Osteosarcomas are characterized by variants in the TP53 tumor suppressor gene.

The prognosis of osteosarcoma has greatly improved, with 5-year survival rates increasing between 1975 and 2010 from 40% to 76% in children younger than 15 years and from 56% to
66% in 15- to 19-year-olds. Prognostic factors for patients with localized disease include site and size of the primary tumor, the presence of metastases at the time of diagnosis, resection adequacy, and tumor response to neoadjuvant chemotherapy.

**Treatment**

For patients with recurrent osteosarcoma, the most important prognostic factor is surgical resectability. There is a 5-year survival rate of 20% to 45% in patients who had a complete resection of metastatic pulmonary tumors and a 20% survival rate for patients with metastatic tumors at other sites.²⁰

**Retinoblastoma**

Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (25%-30%) or nonheritable (70%-75%) tumor.²¹ Cases may be unilateral or bilateral, with bilateral tumor almost always occurring in the heritable type.

**Treatment**

Treatment options depend on the extent of disease. Retinoblastoma is usually confined to the eye, and with current therapy has a high cure rate. However, once disease spreads beyond the eye, survival rates drop significantly; 5-year disease-free survival is reported to be less than 10% in those with extraocular disease, and stage 4B disease (ie, disease metastatic to the central nervous system) has been lethal in virtually all cases reported.²²

The strategy for nonmetastatic disease depends on the disease extent but may include focal therapies (eg, laser photocoagulation, cryotherapy, plaque radiotherapy), intravitreal chemotherapy, intra-arterial chemotherapy, systemic chemotherapy, enucleation, or a combination.²³ For metastatic disease, intensive multimodal therapy with high-dose chemotherapy, with or without radiotherapy, is standard care.

Notes: Other solid tumors of childhood include germ cell tumors, which are considered in another policy. Solid tumors classified as embryonal tumors arising in the central nervous system and central nervous system tumors derived from glial cells (ie, astrocytoma, oligodendroglioma, or glioblastoma multiforme) are addressed in separate medical policies (see Related Policies above).
**Hematopoietic Cell Transplantation**

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs, with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). 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 "naive" 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 HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens using cellular, serologic, or molecular techniques. Human leukocyte antigens refer to the tissue type expressed at class I and class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor (except umbilical cord blood) will match the patient at all or most human leukocyte antigens loci.

**Summary of Evidence**

For individuals who have high-risk or relapsed peripheral neuroblastoma who receive single or tandem autologous HCT, the evidence includes RCTs and systematic reviews of those trials. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. In the pooled analysis, patients with high-risk neuroblastoma treated with first-line therapy with single autologous HCT with myeloablative conditioning had significantly improved event-free survival compared with standard therapy. Similarly, well-designed randomized trials comparing tandem autologous HCT with conventional therapy showed improvements in event-free survival for children with high-risk neuroblastoma. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have high-risk Ewing sarcoma who receive single or tandem autologous HCT, the evidence includes single-arm studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Although early nonrandomized studies were promising, more recent prospective nonrandomized study results have been inconsistent regarding whether HCT extends survival compared with typical conventional
therapy. Additional studies, including a randomized trial, are ongoing, comparing HCT with conventional therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

However, clinical input obtained in 2011 supported the use of single autologous HCT for high-risk Ewing sarcoma, and it is supported by national guidelines from the American Society for Blood and Marrow Transplantation. Also, the use of single autologous HCT is supported by national guidelines for recurrent or refractory Ewing sarcoma. Therefore, autologous HCT may be considered medically necessary for these indications.

For individuals who have rhabdomyosarcoma who receive single autologous HCT, the evidence includes nonrandomized comparative studies and case series. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Available studies have not demonstrated improvements in overall survival or event-free survival with autologous HCT. Additional research is needed to demonstrate a benefit with autologous HCT for pediatric rhabdomyosarcoma. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Wilms tumor who receive single autologous HCT, the evidence includes a meta-analysis of case series and case reports. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Overall four-year survival rates were similar between patients receiving HCT and receiving chemotherapy. There was a trend suggesting that patients with lung-only stage 3 or 4 relapse might benefit from autologous HCT. However, the overall body of evidence is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2017 does not support that the use of autologous HCT for children with advanced-stage Wilms tumor provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice:

Thus, the above indication may be considered investigational.

For individuals who have osteosarcoma who receive single autologous HCT, the evidence includes case reports, case series, and a prospective single-arm study. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. An interim analysis of the prospective single-arm study showed that patients receiving autologous HCT were experiencing lower event-free survival rates than historical controls, resulting in all patients being enrolled in standard of care chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.
Clinical input obtained in 2017 does not support that the use of autologous HCT for children with osteosarcoma provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice:

Thus, the above indication may be considered investigational.

For individuals who have localized retinoblastoma who receive single autologous HCT, the evidence includes no studies. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have metastatic retinoblastoma who receive single autologous HCT, the evidence includes small case series and case reports. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Results from the limited data have suggested that autologous HCT may prolong disease-free survival, particularly in patients without central nervous system involvement (stage 4A). Given the poor prognosis for this indication with conventional therapies, the incremental improvement with autologous HCT might be considered a significant benefit. However, the overall body of evidence is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

However, clinical input obtained in 2017 supports that the following indication provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice:

- Use of autologous HCT for children with metastatic retinoblastoma.

Thus, the above indication may be considered medically necessary considering the suggestive evidence and clinical input support.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 1.
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined Solid Tumor</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NCT00638898</td>
<td>Pilot Study of High-Dose Chemotherapy With Busulfan, Melphalan, and Topotecan Followed by Autologous Hematopoietic Stem Cell Transplant in Advanced Stage and Recurrent Tumors</td>
<td>25</td>
<td>Jun 2019</td>
</tr>
<tr>
<td><strong>Peripheral neuroblastoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01704716</td>
<td>High Risk Neuroblastoma Study 1 of SIOP-Europe (SIOPEN)</td>
<td>3300</td>
<td>Sep 2024 (ongoing)</td>
</tr>
<tr>
<td><strong>Ewing sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00987636</td>
<td>Phase 3, Open Label, Multi-centre, Randomized Controlled International Study in Ewing Sarcoma</td>
<td>1163</td>
<td>Mar 2019</td>
</tr>
<tr>
<td><strong>Retinoblastoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00554788</td>
<td>A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma</td>
<td>60</td>
<td>Jun 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

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

2017 Input

In response to requests, clinical input on autologous hematopoietic cell transplantation for children with metastatic retinoblastoma, advanced-stage Wilms tumor, and osteosarcoma was received from 2 respondents, including 2 physicians from academic centers, while this policy was under review in 2017.
Based on the evidence and independent clinical input, the clinical input supports that the following indications provide a clinically meaningful improvement in the net health outcome and are consistent with generally accepted medical practice:

- Use of autologous hematopoietic cell transplantation for children with metastatic retinoblastoma.

Based on the evidence and independent clinical input, the clinical input does not support whether the following indications provide a clinically meaningful improvement in the net health outcome or are consistent with generally accepted medical practice:

- Use of autologous HCT for children with advanced-stage Wilms tumor.
- Use of autologous HCT for children with osteosarcoma.

**2011 Input**

In response to requests, input was received from 3 academic medical centers and 2 Blue Distinction Centers for Transplants for review in 2011. There was general agreement among reviewers for most of the policy statements with the following exceptions. One reviewer considered autologous hematopoietic cell transplantation (HCT) medically necessary for advanced-stage retinoblastoma. One reviewer did not consider autologous HCT for low- to intermediate-risk Ewing sarcoma investigational but did state that the results of the Euro-Ewing’s phase 3 trial were awaited. Two reviewers agreed with the policy statement that tandem autologous HCT for pediatric solid tumors is investigational, two considered it medically necessary for high-risk neuroblastoma, and a fifth reviewer while agreeing that tandem autologous HCT is considered investigational for pediatric solid tumors also stated that it is considered standard for high-risk neuroblastoma at some centers.

**Practice Guidelines and Position Statements**

*American Society for Blood and Marrow Transplantation*

The American Society for Blood and Marrow Transplantation (2015) published consensus guidelines for clinically appropriate indications for HCT based on best prevailing evidence.\(^{66}\) Indications for HCT in pediatric patients with the solid tumors types addressed in this review are outlined in Table 2.
Table 2. Indications for HCT in Pediatric Patients With Solid Tumors

<table>
<thead>
<tr>
<th>Indication and Disease Status</th>
<th>Allogeneic HCTa</th>
<th>Autologous HCTa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing sarcoma, high risk or relapse</td>
<td>D</td>
<td>S</td>
</tr>
<tr>
<td>Soft tissue sarcoma, high risk or relapse</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Neuroblastoma, high risk or relapse</td>
<td>D</td>
<td>S</td>
</tr>
<tr>
<td>Wilms tumor, relapse</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>Osteosarcoma, high risk</td>
<td>N</td>
<td>C</td>
</tr>
</tbody>
</table>

Adapted from Majhail et al (2015).66

HCT: hematopoietic cell transplantation.

a “Standard of care (S): This category includes indications that are well defined and are generally supported by evidence in the form of high quality clinical trials and/or observational studies (eg, through CIBMTR or EBMT).”

“Standard of care, clinical evidence available (C): This category includes indications for which large clinical trials and observational studies are not available. However, HCT has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. HCT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as ‘Standard of Care’. “Developmental; (D): Developmental indications include diseases where pre-clinical and/or early phase clinical studies show HCT to be a promising treatment option. HCT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as ‘Standard of Care, Clinical Evidence Available’ or ‘Standard of Care’. “Not generally recommended (N): Transplantation is not currently recommended for these indications where evidence and clinical practice do not support the routine use of HCT. The effectiveness of non-transplant therapies for an earlier phase of a disease does not justify the risks of HCT. Alternatively, a meaningful benefit is not expected from the procedure in patients with an advanced phase of a disease. However, this recommendation does not preclude investigation of HCT as a potential treatment and transplantation may be pursued for these indications within the context of a clinical trial.”

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines or comments on HCT related to the cancers addressed in this review are summarized in Table 3. Other tumor types are not addressed in Network guidelines.

Table 3. NCCN Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Tumor Type</th>
<th>Year</th>
<th>NCCN Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone cancer67</td>
<td>Osteosarcoma</td>
<td>v.1.2018</td>
<td>HCT not addressed</td>
</tr>
<tr>
<td>Guideline</td>
<td>Tumor Type</td>
<td>Year</td>
<td>NCCN Comments</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
<td>-------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bone cancer</td>
<td>Ewing sarcoma</td>
<td>v.1.2018</td>
<td>“High dose chemotherapy 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. HDT/SCT has been associated with improved 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.”</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>Rhabdomyosarcoma</td>
<td>v.1.2018</td>
<td>HCT not addressed</td>
</tr>
</tbody>
</table>

HCT: hematopoietic cell transplantation; NCCN: National Comprehensive Cancer Network.

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

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

**References**


investigational as initial treatment of low- or intermediate-risk neuroblastoma.
Multiple cycle high-dose chemotherapy and hematopoietic stem-cell support (i.e.,
tandem or multiple transplants) is considered investigational for treatment of
neuroblastoma. References added. Recommended and reviewed by OAP 11/15/07.

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/31/07</td>
<td>Codes Updated - CPT code 86817 removed as directed by RPIW.</td>
</tr>
</tbody>
</table>
| 06/10/08   | Replace Policy - Policy extensively consolidated and rewritten; updated with literature
             search. References also extensively revised; no changes to policy statements |
| 12/08/09   | Replace Policy - Policy updated with literature search; no change to the policy
             statement. Recommended and reviewed by OAP August 21, 2009. Code 86817 added
             back to the policy.                                                            |
| 02/09/10   | Code Update - New 2010 codes added.                                       |
| 06/08/10   | Replace Policy - Policy updated with NCCN 2010 Guidelines. No change to policy
| 06/13/11   | Replace Policy - Policy presented to OAP for review May 12, 2011. Policy title changed to
             “Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood” from
             “HDC with Hematopoietic Stem-Cell Support for Solid Tumors in Childhood.” ICD-10 codes added to policy. |
| 01/25/12   | Code 38232 added.                                                         |
| 02/09/12   | CPT code 38204 was removed from the policy.                               |
| 06/12/12   | Replace Policy. Policy updated with literature search. Policy statement changed:
             Tandem autologous HSCT, previously considered investigational, may now be
             considered medically necessary for high risk neuroblastoma.                   |
| 09/19/12   | Update Coding Section – ICD-10 codes are now effective 10/01/2014.        |
| 09/28/12   | Update Related Policies – Add 8.01.20-30, 8.01.514 and 8.01.520.           |
| 11/15/12   | Reviewed and recommended by OAP, November 2012.                           |
| 02/01/13   | Update Related Policies, change title of policy 8.01.21.                 |
| 02/15/13   | Update Related Policies, change title of policy 8.01.30.                 |
| 03/20/13   | The following codes were removed from the policy, as they were not suspending and
             just informational: HCPCS J9000-J9999 and Q0083 – Q0085.                      |
| 07/24/13   | Replace policy. Policy updated with literature review; Rationale reorganized.
             References updated, added and renumbered. No change in policy statements.      |
<p>| 09/30/13   | Update Related Policies. Change title to policy 8.01.31.                 |
| 10/18/13   | Update Related Policies. Change title to policy 8.01.17.                 |
| 12/06/13   | Update Related Policies. Remove 8.01.31 as it was archived.               |
| 01/30/14   | Update Related Policies. Change title to 8.01.21.                        |</p>
<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/27/14</td>
<td>Update Related Policies. Change title to 8.01.30.</td>
</tr>
<tr>
<td>03/21/14</td>
<td>Update Related Policies. Remove 8.01.514 as it was deleted.</td>
</tr>
<tr>
<td>04/18/14</td>
<td>Update Related Policies. Delete 8.01.20 and replace with 8.01.529.</td>
</tr>
<tr>
<td>06/09/14</td>
<td>Annual Review. Policy updated with literature search. Policy statements changed. Retinoblastoma added to the list of conditions for which autologous HSCT is considered medically necessary; treatment of recurrent Wilms tumor with HDC or autologous HSCT and tandem autologous HSCT for high-risk neuroblastoma remain medically necessary, but now must be conducted as part of a clinical trial.</td>
</tr>
<tr>
<td>06/24/14</td>
<td>Update Related Policies. Remove 8.01.35, 8.01.42, 8.01.54, then add 8.01.530 and 8.01.532.</td>
</tr>
<tr>
<td>02/03/15</td>
<td>Update Related Policies. Remove 8.01.23, 8.01.28 and 8.01.30.</td>
</tr>
<tr>
<td>06/09/15</td>
<td>Annual Review. Policy updated with literature review; no change in policy statements. Related Policies removed except 7.01.50. ICD-9 and ICD-10 codes removed; these were informational only.</td>
</tr>
<tr>
<td>09/30/16</td>
<td>Coding Update. Remove CPT 86817 from coding table near end of policy.</td>
</tr>
<tr>
<td>11/04/16</td>
<td>Coding Update. Removed codes that are transplant benefit related.</td>
</tr>
<tr>
<td>12/01/16</td>
<td>Annual review, approved November 8, 2016. No changes to policy statement.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Annual Review, approved July 18, 2017. Policy moved into new format. The word stem dropped from the policy title. Retinoblastoma was divided into metastatic retinoblastoma and retinoblastoma without metastases. HCT for metastatic retinoblastoma is now medically necessary. HCT for retinoblastoma without metastases was added as investigational. HCT for late stage Wilms Tumor previously covered as medically necessary is now investigational based upon input from BC/BS association, guidelines from the American Society for Bone Marrow Transplant, UpToDate review, and weak support for use from a single clinician. Tandem autologous HCT for high risk or relapsed neuroblastoma is now covered as medically necessary based upon BCBS coverage and literature review.</td>
</tr>
<tr>
<td>10/08/18</td>
<td>Minor edit, added Documentation Requirements section.</td>
</tr>
<tr>
<td>05/01/19</td>
<td>Annual Review, approved April 2, 2019. Policy updated with literature review through October 2018; reference 55 added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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