



Louisiana

Hematopoietic Cell Transplantation for Solid Tumors of Childhood

Policy # 00064

Original Effective Date: 01/28/2002

Current Effective Date: 07/11/2018

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When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) for the following conditions to be **eligible for coverage**:

- 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.
- Metastatic retinoblastoma.

Based on review of available data, the Company may consider tandem autologous hematopoietic cell transplantation (HCT) for high-risk neuroblastoma to be **eligible for coverage**.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous hematopoietic cell transplantation (HCT) 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 to be **investigational**.*

- Rhabdomyosarcoma (RMS)
- Wilm's tumor
- Osteosarcoma
- Retinoblastoma without metastasis.

Based on review of available data, the Company considers tandem autologous hematopoietic cell transplantation (HCT) for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma, as noted above to be **investigational**.*

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Based on review of available data, the Company considers allogeneic (myeloablative or nonmyeloablative) hematopoietic cell transplantation (HCT) for treatment of pediatric solid tumors to be **investigational**.*

Based on review of available data, the Company considers salvage allogeneic hematopoietic cell transplantation (HCT) for pediatric solid tumors that relapse after autologous transplant or fail to respond to be **investigational**.*

Background/Overview

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 sarcoma/Ewing sarcoma family of tumors (ESFT), Wilms tumor, 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 radiotherapy). 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 HCT, in an effort to improve event-free survival (EFS) and overall survival (OS).

Descriptions of the solid tumors of childhood addressed in this evidence review are as follows.

Peripheral Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood, with approximately 90% of 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, 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, 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 recent 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.

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In the early 1990s, a uniform clinical staging system based on surgical resectability and distant spread, the International Neuroblastoma Staging System (INSS), was adopted by pediatric cooperative groups (see Table 1).

Table 1. International Neuroblastoma Staging System

Stage	Description
1	Localized tumor with complete gross excision, with or without microscopic residual disease; lymph nodes negative for tumor
2A	Localized tumor with incomplete gross excision; lymph nodes negative for tumor
2B	Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor
3	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
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S
4S	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

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

In 2009, the International Neuroblastoma Risk Group proposed a revised staging system, which incorporated pretreatment imaging parameters instead of surgical findings (see Table 2).

Table 2. International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Treatment

In general, most patients with low-stage disease have excellent outcomes with minimal therapy; and with INSS stage-1 disease, most patients can be treated by surgery alone. Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.

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For intermediate-risk disease, moderately intensive multiagent chemotherapy is the mainstay of therapy. Surgery is needed to obtain a diagnosis, and the extent of resection necessary to obtain an optimal outcome is not clearly established. Patients at high risk have historically had very low (<15%) long-term OS. Current therapy for high-risk disease typically includes an aggressive multimodal approach with chemotherapy, surgical resection, and radiotherapy.

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 Sarcoma 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 diagnosis. Included in ESFT are “classic” Ewing sarcoma of bone, extrasosseous Ewing, peripheral primitive neuroectodermal tumor, 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 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 sarcoma typically includes induction chemotherapy, followed by local control with surgery and/or radiation (dependent on tumor size and location), followed by adjuvant chemotherapy. Multiagent chemotherapy, surgery, and radiotherapy have improved PFS in patients with localized disease to 60% to 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% to 30% PFS. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing are tumor location (eg, patients with pelvic primaries have worse outcomes), larger tumor size, and older age of the patient. However, “high-risk” Ewing has not always been consistently defined in the literature.

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.

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Treatment

Specific treatment is based on tumor location, resection, and node status, and may involve surgery, radiotherapy, and chemotherapy. Five-year survival rates for RMS 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.

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. Similarly, postrelapse 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.

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 (see Table 3).

Table 3. National Wilms Tumor Study Staging

Stage	Description
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
III	Residual tumor confined to the abdomen: (a) Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain tumor (b) Diffuse peritoneal contamination by the tumor (c) Implants are found on the peritoneal surfaces (d) Tumor extends beyond the surgical margins either microscopically or grossly (e) Tumor is not completely resectable because of local infiltration into vital structures
IV	Presence of hematogenous metastases or metastases to distant lymph nodes
V	Bilateral renal involvement at the time of initial diagnosis

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.

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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.

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. Cases may be unilateral or bilateral, with bilateral tumors almost always being 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 the extraocular disease, and stage 4B disease (ie, disease metastatic to the central nervous system) has been lethal in virtually all cases reported.

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. For metastatic disease, intensive multimodal therapy with high-dose chemotherapy, with or without radiotherapy, is standard care.

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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 refers 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be

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adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

PERIPHERAL NEUROBLASTOMA

Single Autologous Hematopoietic Cell Transplantation

Systematic Reviews

A 2013 Cochrane review evaluated high-dose chemotherapy (HDC) and autologous HCT for high-risk neuroblastomas. Reviewers identified 3 RCTs that included 739 children with high-risk neuroblastoma (Matthay et al [1999], Berthold et al [2005], Pritchard et al [2005], detailed in the Randomized Controlled Trial section below). The review was updated in 2015 with no new studies identified, although a manuscript reporting additional follow-up data for one of these RCTs was noted. The primary objective was to compare the efficacy of myeloablative therapy with conventional therapy. Selected studies all used the age of 1 year as the cutoff point for pretreatment risk stratification. A statistically significant difference in EFS was observed in favor of myeloablative therapy over conventional chemotherapy or no further treatment (3 studies, 739 patients; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67 to 0.90). A statistically significant difference in overall survival (OS) was reported in favor of myeloablative therapy over conventional chemotherapy or no further treatment (2 studies, 360 patients; HR=0.74; 95% CI, 0.57 to 0.98). When additional follow-up data were included in analyses, the difference in EFS remained statistically significant (3 studies, 739 patients; HR=0.79; 95% CI, 0.70 to 0.90), but the difference in OS was no longer statistically significant (2 studies, 360 patients; HR=0.86; 95% CI, 0.73 to 1.01). Meta-analysis of secondary malignant disease and treatment-related death did not show any statistically significant differences between treatment groups. Data from 1 study (379 patients) showed a significantly higher incidence of renal effects, interstitial pneumonitis, and veno-occlusive disease in the myeloablative group compared with conventional chemotherapy, whereas for serious infections and sepsis, no significant differences between treatment groups were identified. No information on quality of life was reported.

Randomized Controlled Trials

Three well-designed, randomized trials have assessed autologous HCT in the treatment of high-risk neuroblastoma. In a study published in 1999, Matthay et al randomized 129 children with high-risk neuroblastoma to a combination of myeloablative chemotherapy, total body irradiation, and transplantation of autologous bone marrow and compared their outcomes to those of 150 children randomized to intensive nonmyeloablative chemotherapy; both groups underwent a second randomization to receive subsequent 13-cis-retinoic acid (cis-RA) or no further therapy. The 3-year EFS rate among patients assigned to transplantation was 43% versus 27% among those assigned to continuation chemotherapy ($p=0.027$). However, OS rates for both groups did not differ significantly, with 3-year estimates of 43% or 44% for those assigned to transplant and to continued chemotherapy, respectively ($p=0.87$).

Long-term results from this trial were reported in 2009 after a median follow-up of 7.7 years (range, 130 days to 12.8 years). Five-year EFS for patients who underwent autologous transplant was 30% versus 19%

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for those who underwent nonmyeloablative chemotherapy ($p=0.04$). Five-year OS rates from the second randomization of patients who underwent both random assignments were 59% (SD=8%) for autologous transplant/cis-RA, 41% for autologous transplant/no cis-RA, and, for nonmyeloablative chemotherapy, 38% and 36% with and without cis-RA. Authors concluded that myeloablative chemotherapy and autologous HCT resulted in a significantly better 5-year EFS and OS rates.

In a 2005 study, Berthold et al randomized 295 patients with high-risk neuroblastoma to myeloablative therapy (melphalan, etoposide, carboplatin) with autologous HCT or to oral maintenance chemotherapy with cyclophosphamide. The primary end point was EFS, with secondary end points of OS and treatment-related deaths. Intention-to-treat (ITT) analysis showed that patients who received the myeloablative therapy had an increased 3-year EFS compared with the oral maintenance group (47% [95% CI, 38% to 55%] vs 31% [95% CI, 23% to 39%]), but did not have significantly increased 3-year OS (62% [95% CI, 54% to 70%] vs 53% [95% CI, 45% to 62%]; $p=0.088$). Two patients died from therapy-related complications during induction; no patients who received oral maintenance therapy died from treatment-related toxic effects; and 5 patients who received myeloablative therapy died from acute complications related to the therapy.

In 2005, Pritchard et al reported the results of a randomized, multicenter trial that involved 167 children with stage 3 or 4 neuroblastoma treated with standard induction chemotherapy who then underwent surgical resection of their tumor. Sixty-nine percent of the patients ($n=90$) who achieved complete response (CR) or partial response (PR) to the induction chemotherapy were eligible for randomization to HDC (melphalan) with autologous HCT or to no further treatment (NFT). Seventy-two percent ($n=65$) of the eligible children were randomized, with 21 surviving at the time of the analysis (median follow-up, 14.3 years). A significant difference in the 5-year EFS and OS rates were seen in children older than 1 year of age with stage 4 disease (48 children with stage 4; 5-year EFS, 33% for HDC vs 17% for NFT; $p=0.01$).

Observational Studies

The use of HCT in patients with high-risk neuroblastoma has been supported in clinical practice. For example, in 2016, Proust-Houdemont et al reported on a 30-year single-center series including 215 patients with stage 4, high-risk neuroblastoma treated with HDC (busulfan) with HCT. In this cohort, 5-year EFS and OS rates were 35.1% and 40%, respectively, and improved from baseline to the end of reporting period.

Tandem Autologous HCT

Nonrandomized Comparative Studies

In 2010, Sung et al reported on a retrospective analysis of the efficacy of single versus tandem autologous HCT in patients older than 1 year of age newly diagnosed with stage 4 neuroblastoma from 2000 to 2005 who were enrolled in the Korean Society of Pediatric Hematology-Oncology registry. Patients were intended to receive a single ($n=70$) or tandem ($n=71$) autologous HCT at diagnosis; 57 and 59 patients underwent single and tandem transplantation as scheduled, respectively. Between groups, patient characteristics were similar with the exception of a higher proportion in the tandem group having bone metastases. Median follow-up was 56 months (range, 24-88 months) from diagnosis. Transplant-related mortality (TRM)

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occurred in 9 patients in the single transplant group and in 8 in the tandem group (2 after the first transplant and 6 after the second). The ITT survival rate for 5-year EFS for single versus tandem was 31.3% and 51.2%, respectively ($p=0.03$). When the survival analysis only included patients who proceeded to transplant, the probability of relapse-free survival after the first transplant was higher in the tandem group (59.1%, $SD=13.5\%$) than the single group (41.6%, $SD=14.5\%$; $p=0.099$). The difference was statistically significant when the analysis focused on patients who did not achieve a CR before the first transplant (55.7% vs 0%, $p=0.012$). The authors concluded that tandem HCT for high-risk neuroblastoma is superior to single HCT in terms of survival, particularly in patients without CR before HCT.

In 2008, Ladenstein et al reported on more than 4000 transplants for primary (89%) and relapsed (11%) neuroblastoma over 28 years in 27 European countries in the European Group for Blood and Marrow Transplantation registry. Procedures included single autologous ($n=2895$), tandem autologous ($n=455$), and allogeneic HCT ($n=71$). Median age at the time of transplantation was 3.9 years (range, 0.3-62 years), with 77 patients older than age 18 years. Median follow-up from HCT was 9 years. TRM decreased over time in registry patients who only received autologous transplants. Five-year OS rates were 37% for the autologous groups (single and tandem) and 25% for the allogeneic group. Five-year OS for single versus tandem autologous HCT was 38% versus 33%, respectively ($p=0.105$).

Single-Arm Studies

In 2006, George et al reported on a 4-institution, single-arm clinical trial to evaluate tandem autologous HCT in pediatric patients with high-risk neuroblastoma ($n=82$) enrolled between 1994 and 2002. Median age at diagnosis was 35 months (range, 6 months to 18 years). Three- and 5-year OS rates were 74% (95% CI, 62% to 82%) and 64% (95% CI, 52% to 74%), respectively.

In 2002, Kletzel et al reported on a single-center pilot study evaluating the outcomes for 25 consecutive newly diagnosed high-risk neuroblastoma patients and 1 with recurrent disease treated with triple-tandem autologous HCT. After stem cell rescue, patients were treated with radiotherapy to the primary site. Twenty-two of the 26 patients successfully completed induction therapy and were eligible for the triple-tandem consolidation high-dose therapy. Seventeen patients completed all 3 cycles of high-dose therapy and stem cell rescue, 2 patients completed 2 cycles, and 3 patients completed 1 cycle. One toxicity-related death occurred, and 1 patient died from complications of graft failure. Median follow-up was 38 months, and the 3-year EFS and OS rates were 57% and 79%, respectively.

In 2000, Grupp et al reported outcomes for a phase 2 trial involving 55 children with high-risk neuroblastoma who underwent tandem autologous HCT. Five patients completed the first HCT course but not the second. There were 4 toxicity-related deaths. With a median follow-up of 24 months from diagnosis, 3-year EFS was 59%.

Case Series

In 2016, in a retrospective analysis of prospectively collected data, Pasqualini et al reported on a series of 26 patients with very high risk neuroblastoma treated with tandem autologous HCT from 2004 to 2011 at a

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single center. Criteria for “very high risk” included stage 4 neuroblastoma at diagnosis or relapse, age over 1 year at diagnosis, less than a PR of metastases, and more than 3 metaiodobenzylguanidine spots after 2 lines of conventional chemotherapy in patients under 10 years old or no CR of metastases after 1 line of conventional chemotherapy in patients over 10 years old. Median age was 4.4 years (range, 1-15.9 years). Of the 26 patients, 22 were stage 4 at diagnosis; 4 patients had a stage 3 tumor at diagnosis and a metastatic relapse. Three-year EFS and OS rates after diagnosis were 37.3% (95% CI, 21.3% to 56.7%) and 69.0% (95% CI, 49.7% to 83.4%), respectively.

In 2007, Kim et al retrospectively analyzed 36 patients with high-risk (stage 3 or 4) neuroblastoma who underwent a single autologous HCT (n=27) or a tandem autologous HCT (n=9) at a children’s hospital in Seoul, Korea, between 1996 and 2004. Disease-free survival (DFS) of patients who underwent double HCT was similar to that of those who underwent a single autologous HCT (p=0.5).

In 2003, Marcus et al reported on outcomes for 52 children with stage 4 or high-risk stage 3 neuroblastoma treated with induction chemotherapy, surgical resection of the tumor when feasible, local radiotherapy, and consolidation with tandem autologous HCT. Radiotherapy was given if gross or microscopic residual disease was present before the myeloablative cycles (n=37). Of the 52 consecutively treated patients analyzed, 44 underwent both transplants, 6 underwent a single transplant, and 2 progressed during induction. The 3-year EFS was 63%, with a median follow-up of 29.5 months.

In 2005, von Allmen et al reported on a retrospective series from the same center as Marcus et al, with some overlap in patients. The updated series included 76 patients with previously untreated high-risk stage 3 or 4 neuroblastoma treated with aggressive surgical resection with or without local radiotherapy followed by tandem autologous HDC and stem cell rescue. Overall EFS for the series was 56%.

Section Summary: Single Autologous and Tandem Hematopoietic Cell Transplantation for Peripheral Neuroblastoma

No studies directly comparing single autologous and tandem autologous HCT for high-risk neuroblastoma have been published. Randomized trials comparing single autologous HCT with conventional chemotherapy have reported EFS rates for the patients who underwent HCT ranging from 43% to 47% at 3 years and 30% at 5 years. Case series on the use of tandem autologous for high-risk neuroblastoma have reported 3-year EFS rates ranging from 57% to 63%. A retrospective analysis of a registry of patients with newly diagnosed high-risk neuroblastoma reported 5-year EFS rates for single and tandem autologous HCT of 31% and 51%, respectively (p=0.03).

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EWING SARCOMA FAMILY OF TUMORS

Single Autologous HCT

During the 1980s and 1990s, several small series, case reports, and a report from the European Bone Marrow Transplant Registry suggested that autologous HCT could improve outcomes for patients with high-risk ESFT. These early results support use of HCT for high-risk ESFT.

Subsequently, in 2001, Meyers et al reported on a prospective study with autologous HCT in 32 patients with newly diagnosed Ewing sarcoma metastatic to bone and/or bone marrow. Induction therapy consisted of 5 cycles of cyclophosphamide-doxorubicin-vincristine, alternating with ifosfamide-etoposide. Twenty-three patients proceeded to the consolidation phase with melphalan, etoposide, total body irradiation, and autologous HCT (of the 9 patients who did not proceed, 2 were secondary to toxicity and 4 to progressive disease). Three patients died during the HDC phase. Two-year EFS for all eligible patients was 20% and 24% for the 29 patients who received the high-dose consolidation therapy. Trialists concluded that consolidation with HDC, total body irradiation, and autologous stem cell support failed to improve EFS for this cohort of patients compared with a similar group of patients treated with conventional therapy. Authors noted that their findings differed from some previous studies, and that the previous studies suffered from heterogeneous patient populations. They concluded that future trials of autologous HCT must be conducted prospectively, identify a group at high risk for failure, and enroll all patients in the study at the same point in therapy.

Gardner et al (2008) reported the results of 116 patients with Ewing sarcoma who underwent autologous HCT (80 as first-line therapy, 36 for recurrent disease) between 1989 and 2000. Five-year rates of PFS in patients who received HCT as first-line therapy were 49% (95% CI, 30% to 69%) for those with localized disease at diagnosis and 34% (95% CI, 22% to 47%) for those with metastatic disease at diagnosis. For the population with localized disease at diagnosis and recurrent disease, the 5-year probability of PFS was 14% (95% CI, 3% to 30%). The authors concluded that PFS rates after autologous HCT were comparable with rates seen in patients with similar disease characteristics treated with conventional therapy.

In 2010, Ladenstein et al reported on patients with primary disseminated multifocal Ewing sarcoma (PDMES) who were included in the Euro-EWING 99 trial. From 1999 to 2005, 281 patients with PDMES were enrolled in the Euro-EWING 99 R3 study; the Euro-EWING 99 committee stopped enrollment to this group and release the data. Median age was 16.2 years (range, 0.4-49 years). Patients with isolated lung metastases were not part of the analysis. The recommended treatment consisted of induction chemotherapy, HDC, autologous HCT, and local treatment to the primary tumor (surgery and/or radiation or neither). Induction therapy was completed by 250 (89%) of patients. One hundred sixty-nine (60%) of the patients proceeded to HCT. One patient died during induction therapy from sepsis. HDC TRM consisted of 3 patients dying within the first 100 days after high-dose therapy—1 from acute respiratory distress syndrome and 2 from severe veno-occlusive disease and septicemia; late deaths included 3 patients who died 1 to 1.5 years after high-dose therapy. After a median follow-up of 3.8 years, the estimated 3-year EFS and OS rates for all 281 patients were 27% and 34%, respectively.

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Tandem Autologous HCT

In 2015, Loschi et al reported on a series of 18 patients with PDMES under age 25 treated with tandem HCT at a single institution from 2002 to 2009. Of the 18 patients with PDMES planned for tandem HCT, 15 (83%) received the first HCT, and 13 (72%) received the full-tandem HCT program, due to progressive disease before stem cell harvest could be obtained. Eleven patients had no disease progression by the end of the HCT program, but 9 of the 11 had relapsed, at a median delay of 6.2 months (range, 2.5-14.1 months). Median EFS and OS rates were 13.5 and 17.3 months, respectively.

Section Summary: Single Autologous and Tandem HCT for Ewing Sarcoma Family of Tumors

Studies of HCT in patients with ESFT are characterized by small numbers of patients, and comparisons across studies were difficult for several reasons. Within each report, patients could have received a variety of chemotherapeutic regimens, and many studies did not share the same patient eligibility criteria (and in some, the definition of high risk included patients with criteria that did not result in inferior prognosis). In addition, some studies used allogeneic HCT. The risk-adjusted system used in Euro-EWING 99 may allow best selection of patients appropriate for treatment.

RHABDOMYOSARCOMA

Weigel et al (2001) reviewed and summarized published evidence on the role of autologous HCT in the treatment of metastatic or recurrent RMS from 22 studies (total N=389 patients). Based on all of the evidence analyzing EFS and OS rates, they concluded that there was no significant advantage to undergoing this type of treatment.

McDowell et al (2010) reported on the results of the International Society of Paediatric Oncology study MMT-98, for pediatric patients from 48 centers with metastatic RMS entered into the study from 1998 to 2005. A total of 146 patients enrolled (age range, 6 months to 18 years). Patients were risk-stratified and treated accordingly. One hundred one patients were considered poor-risk (poor-risk group) if they were older than 10 years of age or had bone marrow or bone metastases. Planned therapy for the poor-risk group was induction therapy, sequential HDC, peripheral blood autologous HCT, and maintenance therapy. Seventy-nine (78.2%) of the 101 poor-risk patients underwent the high-dose therapy, after which 67.1% achieved a PR or CR. Sixty-seven of the 101 poor-risk patients received local treatment—37 radiotherapy alone, 10 surgery alone, and 20 both modalities. No treatment-related deaths were reported in the poor-risk group. Three- and 5-year EFS rates for the poor-risk group were 16.5% and 14.9%, respectively, with 3- and 5-year OS rates of 23.7% and 17.9%, respectively (HR=2.46; 95% CI, 1.51 to 4.03; $p < 0.001$).

Klingebl et al (2008) prospectively compared the efficacy of 2 HDC treatments followed by autologous stem cell rescue with an oral maintenance treatment in 96 children with stage 4 soft tissue sarcoma (88 of whom had RMS). Five-year OS probability for the whole group was 0.52 (SD=0.14) for the patients who received OMT (n=51) and 0.27 (SD=0.13) for the transplant group (n=45; $p=0.03$). For the patients with RMS, 5-year OS probability was 0.52 (SD=0.16) with OMT and 0.15 (SD=0.12) with transplant ($p=0.001$). The authors concluded that transplant failed to improve prognosis in metastatic soft tissue sarcoma but that OMT could be a promising alternative.

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Carli et al (1999) conducted a prospective nonrandomized study of 52 patients with metastatic RMS, who were in CR after induction therapy and subsequently received HDC (megatherapy) and autologous HCT, and compared them with 44 patients who were in remission after induction therapy who subsequently received conventional chemotherapy. No significant differences existed between groups (ie, clinical characteristics, induction chemotherapy received, sites of primary tumor, histologic subtype, age, presence/extent of metastases). Three-year EFS and OS rates were 29.7% and 40%, respectively, for the autologous HCT group and 19.2% and 27.7%, respectively, for the chemotherapy group. Differences were not statistically significant for EFS ($p=0.3$) or OS ($p=0.2$). Median time to relapse after chemotherapy was 168 days for the autologous HCT group and 104 days for the standard chemotherapy group ($p=0.05$). Although the use of autologous HCT delayed time to relapse, there was no clear survival benefit compared with conventional chemotherapy.

Section Summary: Rhabdomyosarcoma

Autologous HCT has been evaluated in a limited number of patients with high-risk RMS (stage 4 or relapsed) in whom CR was achieved after standard induction therapy. The evidence is relatively scarce, due in part to the rarity of the condition. The role of stem cell transplantation of any type for this cancer has not been established.

WILMS TUMOR

A 2010 individual patient data meta-analysis reported on the efficacy of autologous HCT in recurrent Wilms tumor for studies published between 1984 and 2008 that reported survival data. Six studies were included (total $N=100$ patients). Patient characteristics and treatment methods were similar across studies, although there was variation in the preparative regimens used. Patients were between the ages of 11 months and 16 years and had similar primary tumor stage, relapse location, and time to relapse. The 4-year OS rate among the 100 patients was 54.1% (95% CI, 42.8%-64.1%), and the 4-year EFS rate (based on 79 patients) was 50.0% (95% CI, 37.9%-60.9%). In multivariate analysis, site of relapse and histology were important predictors for survival; patients who did not have a lung-only relapse were at approximately 3 times higher risk of death or recurrence ($HR=3.5$) than patients who relapsed in the lungs only ($HR=2.4$), and the patients with unfavorable histology had approximately twice the risk of death compared with those with favorable histology. For all 6 studies, reviewers compared the survival rates for patients who received autologous HCT with patients who received conventional chemotherapy. In general, the chemotherapy-treated patients had similar or improved 4-year survival rates compared with the HCT group; however, there was a suggestion that patients with lung-only stage 3 and 4 relapses could benefit from autologous HCT; they had a 21.7% survival advantage over chemotherapy (however, the confidence interval ranges were very wide): 4-year OS rates for the stage 3 and 4 patients with lung-only relapse treated with HCT were 74.5% (95% CI, 51.7% to 87.7%) and 52.8% (95% CI, 29.7% to 71.5%) for chemotherapy.

Section Summary: Wilms Tumor

The evidence on the use of autologous HCT for high-risk Wilms tumor consists of small series or case reports. For some subgroups—particularly patients with lung-only stage 3 and 4 relapses—some analyses have suggested that HCT could be associated with a survival benefit.

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OSTEOSARCOMA

Venkatramani et al (2016) reported on outcomes from a protocol in which patients with newly diagnosed, biopsy-proven high-grade osteosarcoma with less than 90% tumor necrosis after preoperative chemotherapy were treated with 3 courses of HDC plus autologous HCT. The study enrolled 52 patients with localized osteosarcoma, most commonly of the femur (52%) from 1999 to 2006 who underwent definitive surgery; 6 patients withdrew prior to surgery, and 6 after surgery. Under the study's initial protocol, those with less than 90% tumor necrosis were intended for HCT following HDC with melphalan and cyclophosphamide, and those with good tumor response were allocated to standard chemotherapy. However, after the first 18 patients received HCT, an interim analysis showed a 2-year EFS rate of 41%, which was less than the objective of 75% EFS compared with historical data of 55% by treating 48 patients with nonmetastatic disease who showed less than 90% necrosis following preoperative chemotherapy. Subsequently, all patients were enrolled in the standard therapy arm. Forty patients were evaluable after a median follow-up of 39 months. The 5-year EFS and OS rates were 62% (95% CI, 36% to 80%) and 74% (95% CI, 44% to 90%), respectively, for patients treated on the standard chemotherapy arm. The 5-year EFS and OS rates were 28% (95% CI, 10% to 49%) and 48% (95% CI, 23% to 69%), respectively, for patients treated on the HCT arm.

Hong et al (2015) reported on a retrospective series of 19 patients with high-risk osteosarcoma treated with autologous HCT at a single center from 2006 to 2013. Median age at diagnosis was 11.8 years (range, 5.4-15.7 years). The indications for HCT were tumor necrosis less than 90% (n=8), initial metastasis (n=2), relapse (n=2), or a combination of tumor necrosis less than 90%, initial metastasis, and/or progression (n=6). At a mean follow-up of 31 months (range, 1-91 months), the OS rate was 78.3%, and the EFS rate was 67.4%.

Additional small series and case reports have examined the use of autologous HCT in osteosarcoma. Autologous HCT has been successful in inducing short-lasting remissions but has not shown an increase in survival.

Section Summary: Osteosarcoma

The evidence on the use of autologous HCT for treatment of osteosarcoma is limited to case series and a prospective single-arm study. An interim analysis of the single-arm study showed that patients receiving autologous HCT were experiencing lower event-free survival rates than historical controls, resulting in all patients enrolling in the standard of care chemotherapy arm for the remainder of the study.

RETINOBLASTOMA

Localized Retinoblastoma

No studies focusing on autologous HCT for patients with localized retinoblastoma were identified in literature searches.

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Metastatic Retinoblastoma

Most studies of autologous HCT for metastatic retinoblastoma have been very small series or case reports. More recently, Dunkel et al (2010) reported on outcomes for 15 consecutive patients with stage 4A metastatic retinoblastoma who presented between 1993 and 2006 and were treated with HDC and autologous HCT. Twelve patients had unilateral retinoblastoma, and three had bilateral disease. Metastatic disease was not detected at diagnosis but became clinically evident at a median of 6 months (range, 1-82 months) postenucleation. Patients had metastatic disease to bone marrow (n=14), bone (n=10), the orbit (n=9), and/or the liver (n=4). Two patients progressed before HCT and died. Thirteen patients underwent HCT, and 10 are retinoblastoma-free in first remission at a median follow-up of 103 months (range, 34-202 months). Three patients experienced recurrence 14 to 20 months postdiagnosis of metastatic disease, (2 in the central nervous system [CNS], 1 in the mandible), and all died of their disease. Five-year retinoblastoma-free survival and EFS rates were 67% (95% CI, 38% to 85%) and 59% (31% to 79%), respectively. Six of the 10 patients who survived received radiotherapy. Three patients developed secondary osteosarcoma at 4, 9, and 14 years postdiagnosis of metastatic disease, 2 in previously irradiated fields, and 1 in a nonirradiated field. The authors concluded that HCT was curative for most patients treated in their study with stage 4A retinoblastoma.

Dunkel et al (2010) also reported on outcomes for 8 patients diagnosed with stage 4B retinoblastoma between 2000 and 2006 treated with the intention of autologous HCT. Seven patients had leptomeningeal disease and one had only direct extension to the CNS via the optic nerve. At the time of diagnosis of intraocular retinoblastoma, 3 patients already had stage 4B disease; the other 5 patients developed metastatic disease at a median of 12 months (range, 3-69 months). Two patients progressed before HCT, and 1 patient died due to toxicity during induction chemotherapy. Of the 5 patients who underwent HCT, 2 are event-free at 40 and 101 months. One of the event-free survivors received radiotherapy (external-beam plus intrathecal radioimmunotherapy), and the other did not receive any radiotherapy. Three patients had tumor recurrence at 3, 7, and 10 months post-HCT. The authors concluded that HCT could be beneficial for some patients with stage 4B retinoblastoma, but longer follow-up would be necessary to determine whether it is curative in this population.

Section Summary: Localized and Metastatic Retinoblastoma

There is a lack of evidence evaluating use of autologous HCT for localized retinoblastoma.

The results have been promising regarding prolonging disease-free survival in patients with metastatic retinoblastoma, particularly those without CNS involvement (stage 4A). Given that clinical prognosis is very poor for patients with metastases, results showing the survival of some patients for three or more years after HCT might provide evidence to demonstrate a benefit in survival. The role of stem cell transplantation has not been established in the therapy of patients with localized retinoblastoma.

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COMPARATIVE EFFECTIVENESS REVIEW

In 2012, Blue Cross and Blue Shield Association prepared a comparative effectiveness review on the use of HCT in the pediatric population for the Agency for Healthcare Research and Quality. The following conclusions were offered:

- Neuroblastoma: The body of evidence on OS with tandem HCT compared with single HCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.
- ESFT: The low-strength evidence on OS suggested no benefit with single HCT compared with conventional therapy for the treatment of high-risk ESFT.
 - The body of evidence on OS with tandem HCT compared with single HCT for the treatment of high-risk ESFT and OS was insufficient to draw conclusions.
- Rhabdomyosarcoma: The moderate-strength evidence on OS suggested no benefit with single HCT compared with conventional therapy for the treatment of high-risk metastatic RMS.
 - The body of evidence on OS with single HCT compared with conventional therapy for the treatment of high-risk RMS of mixed tumor type was insufficient to draw conclusions.
 - The body of evidence on OS with single HCT compared with conventional therapy for the treatment of congenital alveolar RMS, cranial parameningeal RMS with metastasis or the use of allogeneic transplantation for metastatic RMS was insufficient to draw conclusions.
- Wilms tumor: The low-strength evidence on OS suggested no benefit with single HCT compared with conventional therapy for the treatment of high-risk relapsed Wilms tumor.
- Osteosarcoma was not addressed.
- Retinoblastoma: The low-strength evidence on OS suggested no benefit with single HCT compared with conventional therapy for the treatment of extraocular retinoblastoma with CNS involvement.
 - The body of evidence on OS with single HCT compared with conventional therapy for the treatment of extraocular retinoblastoma without CNS involvement was insufficient to draw conclusions.
 - The body of evidence on OS with single HCT compared with conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was insufficient to draw conclusions.

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.

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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.

For individuals who have rhabdomyosarcoma who receive single autologous HCT, the evidence includes nonrandomized comparative studies and case series. 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 4-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.

For individuals who have osteosarcoma who receive single autologous HCT, the evidence includes case reports, case series, and a prospective single-arm study. 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.

For individuals who have localized retinoblastoma who receive single autologous HCT, the evidence includes no studies. 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.

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Policy History

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- 12/06/2001 Medical Policy Committee review
- 01/28/2002 Managed Care Advisory Council approval
- 05/07/2004 Medical Director review
- 05/18/2004 Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Pediatric Solid Tumors policy separated from current HDC with Hematopoietic Stem Cell Support policy. No substance change to policy.
- 06/28/2004 Managed Care Advisory Council approval
- 05/03/2005 Medical Director review. Format revision. No substance change to policy.
- 05/17/2005 Medical Policy Committee review. Policy statement language changed from, “may consider HDC and autologous or syngeneic SCS to treat recurrent or refractory Ewing’s sarcoma to be eligible for coverage” to; “Based on review of available data, the Company may consider HDC and autologous or syngeneic SCS to consolidate remissions of poor-risk Ewing’s sarcoma, or as salvage therapy for those with residual, recurrent or refractory disease to be eligible for coverage.” Patient selection criteria added.
- 05/23/2005 Managed Care Advisory Council approval
- 08/02/2006 Medical Director review
- 08/09/2006 Medical Policy Committee approval. Format revisions, FDA and other governmental regulatory approval added. References updated. Coverage eligibility unchanged.
- 06/13/2007 Medical Director review
- 06/20/2007 Medical Policy Committee approval. Policy updated with literature review. Policy statement added to indicate that multiple cycle high-dose chemotherapy and hematopoietic stem-cell support is considered to be investigational for the treatment of neuroblastoma.
- 07/02/2008 Medical Director review
- 07/16/2008 Medical Policy Committee approval
- 06/04/2009 Medical Director review
- 06/17/2009 Medical Policy Committee approval. Changed title from “High-Dose Chemotherapy with Stem Cell Support for Solid Tumors of Childhood” to “High-Dose Chemotherapy with Hematopoietic Stem Cell Support for Solid Tumors of Childhood”. Changed “poor-risk Ewing’s sarcoma” to “high-risk Ewing’s sarcoma” in the “When Services May Be Eligible for Coverage” section and under the “Patient Selection Criteria.” Extensive changes made to “Background/Overview, FDA, Rationale and References” sections of the policy. No change to coverage eligibility.
- 06/03/2010 Medical Policy Committee review
- 06/16/2010 Medical Policy Implementation Committee approval. Changed title from “High-Dose Chemotherapy with Hematopoietic Stem Cell Support for Support for Solid Tumors of Childhood” to “Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood”. Changed all “high-dose chemotherapy with stem cell support” verbiage to “hematopoietic stem cell transplantation” throughout the coverage section of the policy. Coverage eligibility unchanged.
- 06/02/2011 Medical Policy Committee review

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06/15/2011	Medical Policy Implementation Committee approval. Investigational statement modified to specify that “tandem autologous-autologous hematopoietic stem cell transplantation for treatment of pediatric solid tumors” is investigational. Added that allogeneic (myeloablative or nonmyeloablative) hematopoietic stem cell transplantation for treatment of pediatric solid tumors is investigational.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Policy updated and reformatted.
03/04/2013	Coding updated
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. The coverage statements were modified to state specifically that tandem autologous HSCT for high-risk neuroblastoma is considered to be eligible for coverage, but is investigational for all other indications.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. Changed “hematopoietic stem cell transplantation” to “hematopoietic cell transplantation” per NCCN terminology change. Based on clinical input, “metastatic retinoblastoma” added to first medically necessary statement. In first investigational statement, “retinoblastoma” changed to “retinoblastoma without metastases.”
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date:	07/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C40.00-C40.092 C41.0-C41.9 C47.0 C47.10-C47.22
	C47.3-C47.9 C49.0 C49.10-C49.22 C49.3-C49.9
	C64.1-C64.9 C69.20-C69.22 C74.00-C74.12 C74.90-C74.92

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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