Hematopoietic Cell Transplantation for Solid Tumors of Childhood

Policy # 00064
Original Effective Date: 01/28/2002
Current Effective Date: 08/09/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma is addressed separately in medical policy 00063.

When Services Are 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.***

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.***

Policy Guidelines

This policy addresses peripheral neuroblastoma arising from the peripheral nervous system (ie, neuroblastoma, ganglioneuroblastoma, ganglioneuroma).

Hematopoietic cell transplantation refers to any source of stem cells, ie, autologous, allogeneic, syngeneic, or umbilical cord blood.

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

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

Background/Overview

Solid Tumors of Childhood

Hematopoietic Cell Transplantation for Solid Tumors of Childhood

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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, rhabdomyosarcoma, 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 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 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, 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 frequently occurs 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 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 (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 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 age older than one 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 (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 the 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. Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.

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 established. 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.

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 (E26 transformation-specific) 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, extra osseous 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 radiotherapy (dependent on tumor size and location), followed by adjuvant chemotherapy. Multiagent chemotherapy, surgery, and radiotherapy have improved progression-free survival rates in patients with the 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% progression-free survival. 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
Rhabdomyosarcoma, 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.

Treatment
Specific treatment is based on tumor location, resection, and node status, and may involve surgery, radiotherapy, and chemotherapy. 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.

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, post relapse mortality is very high. The prognosis of the 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

Stage	Description
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.

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-yearolds. 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; five-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.

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.

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, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale/Source

Hematopoietic cell transplantation 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.

For individuals who have high-risk or relapsed peripheral neuroblastoma who receive single or tandem autologous HCT, the evidence includes randomized controlled trials, systematic reviews of those trials, and observational studies. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related mortality (TRM) 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 (EFS) compared with standard therapy. Similarly, well-designed randomized trials comparing tandem autologous HCT with conventional therapy showed improvements in EFS for children with high-risk neuroblastoma. The evidence is sufficient to determine that the technology results in an 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. The relevant outcomes are OS, DSS, and TRM 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 that the technology results in an improvement in the net health outcome.

For individuals who have rhabdomyosarcoma who receive single autologous HCT, the evidence includes nonrandomized comparative studies and case series. The relevant outcomes are OS, DSF, and TRM and morbidity. Available studies have not demonstrated improvements in OS or EFS with autologous HCT. Additional research is needed to demonstrate a benefit with autologous HCT for pediatric rhabdomyosarcoma. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Wilms tumor who receive single autologous HCT, the evidence includes a retrospective analysis, meta-analysis of case series, and case reports. The relevant outcomes are OS, DSS, and TRM 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 that the technology results in an improvement in the net health outcome.

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 OS, DSF, and TRM and morbidity. An interim analysis of the prospective single-arm study showed that patients receiving autologous HCT were experiencing lower EFS rates than historical controls, resulting in all patients being enrolled in the standard of care chemotherapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized retinoblastoma who receive single autologous HCT, the evidence includes no studies. The relevant outcomes are OS, DSS, and TRM and morbidity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have metastatic retinoblastoma who receive single autologous HCT, the evidence includes small case series and case reports and a systematic review and meta-analysis. The relevant outcomes are OS, DSS, and TRM 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 that the technology results in an improvement in the net health outcome.

2017 Input
Clinical input was sought to help determine whether the use of autologous HCT for individuals with advanced-stage Wilms tumor, osteosarcoma, and metastatic retinoblastoma would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 2 physicians with academic medical center affiliation.

For individuals who have advanced-stage Wilms tumor who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have osteosarcoma who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have metastatic retinoblastoma who receive autologous HCT, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice.

2011 Input
Clinical input was sought to help determine whether the use of single autologous HCT for individuals with high-risk Ewing sarcoma would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 academic medical centers and 2 Blue Distinction Centers for Transplants.

For individuals who have high-risk Ewing sarcoma who receive single autologous HCT, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice. 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.

Supplemental Information

Clinical Input 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

Clinical input was sought to help determine whether the use of autologous HCT for individuals with advanced-stage Wilms tumor, osteosarcoma, and retinoblastoma would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 2 physicians with academic medical center affiliation.

For individuals who have advanced-stage Wilms tumor who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have osteosarcoma who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have metastatic retinoblastoma who receive autologous HCT, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice.

2011 Input
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For individuals who have high-risk Ewing sarcoma who receive single autologous HCT, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice. 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.

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) published consensus guidelines for clinically appropriate indications for HCT based on best prevailing evidence. Indications for HCT in pediatric patients with the solid tumors types addressed in this review are outlined in Table 4.

Table 4. Indications for HCT in Pediatric Patients with Solid Tumors

Indication and Disease Status	Allogeneic HCT[a]	Autologous HCT[a]
Ewing sarcoma, high risk or relapse	D	S
Soft tissue sarcoma, high risk or relapse	D	D
Neuroblastoma, high risk or relapse	D	S
Wilms tumor, relapse	N	C
Osteosarcoma, high risk	N	C

Adapted from Majhail et al (2015).
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 5. Other tumor types are not addressed in Network guidelines.

Table 5. NCCN Guidelines

Guideline	Tumor Type	Year	NCCN Comments
Bone cancer	Osteosarcoma	v.1.2021	"The safety and efficacy of HDT/HCT in patients with locally advanced, metastatic, or relapsed osteosarcoma have also been evaluated. In the Italian Sarcoma Group study, treatment with carboplatin and etoposide was followed by stem cell rescue, combined with surgery-induced complete response

			in chemosensitive disease. Transplant-related mortality was 3.1%. The 3-year OS and DFS rates were 20% and 12%, respectively. The efficacy of this approach in patients with high-risk disease is yet to be determined in prospective randomized studies."
Bone cancer	Ewing sarcoma	v.1.2021	"High dose chemotherapy followed by stem cell transplant (HDT/H CT) has been evaluated in patients with localized as well as metastatic disease. HDT/H CT has been associated with potential survival benefit in patients with non-metastatic disease. However, studies that have evaluated HDT/H CT in patients with primary metastatic disease have shown conflicting results…. HDT/H CT 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."
Soft tissue sarcoma	Rhabdomyosarcoma	v.1.2021	HCT not addressed

DFS: disease-free survival; HCT: hematopoietic cell transplantation; HDT: high-dose therapy; NCCN: National Comprehensive Cancer Network; OS: overall survival.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Combined solid tumor			
NCT00638898	Pilot Study of High-Dose Chemotherapy With Busulfan, Melphalan, and Topotecan Followed by Autologous Hematopoietic Stem Cell Transplant in Advanced Stage and Recurrent Tumors	25	Sep 2021*
NCT04530487	A Pilot Study of Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric and Adolescent-Young Adults Patients With High Risk Solid Tumors	40	May 2025
Peripheral neuroblastoma			
NCT01704716	High Risk Neuroblastoma Study 1 of SIOP-Europe (SIOPEN)	3300	Sep 202 6(ongoing)
Ewing sarcoma			
NCT00987636	Phase 3, Open Label, Multi-centre, Randomized Controlled International Study in Ewing Sarcoma	1163	Mar 2019**
Retinoblastoma			
NCT00554788	A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma	60	Jun 2018***

NCT: national clinical trial.
*= Active, not recruiting; no results posted.**=Completed, no results posted.***=Results posted on www.clinicaltrials.gov website, not yet published.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood", 8.01.34, February 2021.

2. Stewart E, Federico S, Karlstrom A, et al. The Childhood Solid Tumor Network: A new resource for the developmental biology and oncology research communities. Dev Biol. Mar 15 2016; 411(2): 287-293. PMID 26068307
3. Hale GA. Autologous hematopoietic stem cell transplantation for pediatric solid tumors. Expert Rev Anticancer Ther. Oct 2005; 5(5): 835-46. PMID 16221053
4. Shimada H, Ambros IM, Dehner LP, et al. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. Cancer. Jul 15 1999; 86(2): 349-63. PMID 10421272
5. Tang XX, Zhao H, Kung B, et al. The MYCN enigma: significance of MYCN expression in neuroblastoma. Cancer Res. Mar 01 2006; 66(5): 2826-33. PMID 16510605
6. Attiyeh EF, London WB, Mosse YP, et al. Chromosome 1p and 11q deletions and outcome in neuroblastoma. N Engl J Med. Nov 24 2005; 353(21): 2243-53. PMID 16306521
7. Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. J Clin Oncol. Jan 10 2009; 27(2): 298-303. PMID 19047290
8. Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. Oncologist. 2003; 8(3): 278-92. PMID 12773750
9. Baker DL, Schmidt ML, Cohn SL, et al. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. N Engl J Med. Sep 30 2010; 363(14): 1313-23. PMID 20879880
10. Mullassery D, Farrelly P, Losty PD. Does aggressive surgical resection improve survival in advanced stage 3 and 4 neuroblastoma? A systematic review and meta-analysis. Pediatr Hematol Oncol. Nov 2014; 31(8): 703-16. PMID 25247398
11. Laprie A, Michon J, Hartmann O, et al. High-dose chemotherapy followed by locoregional irradiation improves the outcome of patients with international neuroblastoma staging system Stage II and III neuroblastoma with MYCN amplification. Cancer. Sep 01 2004; 101(5): 1081-9. PMID 15329919
12. Barker LM, Pendergrass TW, Sanders JE, et al. Survival after recurrence of Ewing's sarcoma family of tumors. J Clin Oncol. Jul 01 2005; 23(19): 4354-62. PMID 15781881
13. National Cancer Institute (NCI). Physician Data Query (PDQ): Childhood rhabdomyosarcoma treatment. 2020; https://www.cancer.gov/types/soft-tissue-sarcoma/hp/rhabdomyosarcoma-treatment-pdq.
14. Raney RB, Anderson JR, Barr FG, et al. Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of intergroup rhabdomyosarcoma study group

experience and rationale for Intergroup Rhabdomyosarcoma Study V. J Pediatr Hematol Oncol. May 2001; 23(4): 215-20. PMID 11846299
15. Admiraal R, van der Paardt M, Kobes J, et al. High-dose chemotherapy for children and young adults with stage IV rhabdomyosarcoma. Cochrane Database Syst Rev. Dec 08 2010; (12): CD006669. PMID 21154373
16. Koscielniak E, Klingebiel TH, Peters C, et al. Do patients with metastatic and recurrent rhabdomyosarcoma benefit from high-dose therapy with hematopoietic rescue? Report of the German/Austrian Pediatric Bone Marrow Transplantation Group. Bone Marrow Transplant. Feb 1997; 19(3): 227-31. PMID 9028550
17. Metzger ML, Dome JS. Current therapy for Wilms' tumor. Oncologist. Nov-Dec 2005; 10(10): 815-26. PMID 16314292
18. Campbell AD, Cohn SL, Reynolds M, et al. Treatment of relapsed Wilms' tumor with high-dose therapy and autologous hematopoietic stem-cell rescue: the experience at Children's Memorial Hospital. J Clin Oncol. Jul 15 2004; 22(14): 2885-90. PMID 15254057
19. Dallorso S, Dini G, Faraci M, et al. SCT for Wilms' tumour. Bone Marrow Transplant. Jun 2008; 41 Suppl 2: S128-30. PMID 18545233
20. National Cancer Institute (NCI). Physician Data Query (PDQ): Osteosarcoma and Malignant fibrous histiocytoma of bone treatment. 2020; https://www.cancer.gov/types/bone/hp/osteosarcoma-treatment-pdq.
21. National Cancer Institute (NCI). Physician Data Query (PDQ): Retinoblastoma treatment: health professional version. 2020; https://www.cancer.gov/types/retinoblastoma/hp/retinoblastoma-treatment-pdq.
22. Dunkel IJ, Chan HS, Jubran R, et al. High-dose chemotherapy with autologous hematopoietic stem cell rescue for stage 4B retinoblastoma. Pediatr Blood Cancer. Jul 15 2010; 55(1): 149-52. PMID 20486181
23. Abramson DH, Shields CL, Munier FL, et al. Treatment of Retinoblastoma in 2015: Agreement and Disagreement. JAMA Ophthalmol. Nov 2015; 133(11): 1341-7. PMID 26378747
24. Yalcin B, Kremer LC, Caron HN, et al. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Syst Rev. Aug 22 2013; (8): CD006301. PMID 23970444
25. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N Engl J Med. Oct 14 1999; 341(16): 1165-73. PMID 10519894

26. Berthold F, Boos J, Burdach S, et al. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial. Lancet Oncol. Sep 2005; 6(9): 649-58. PMID 16129365
27. Pritchard J, Cotterill SJ, Germond SM, et al. High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. Pediatr Blood Cancer. Apr 2005; 44(4): 348-57. PMID 15546135
28. Yalcin B, Kremer LC, van Dalen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Syst Rev. Oct 05 2015; (10): CD006301. PMID 26436598
29. Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. J Clin Oncol. Mar 01 2009; 27(7): 1007-13. PMID 19171716
30. Proust-Houdemont S, Pasqualini C, Blanchard P, et al. Busulfan-melphalan in high-risk neuroblastoma: the 30-year experience of a single institution. Bone Marrow Transplant. Aug 2016; 51(8): 1076-81. PMID 27042850
31. Giardino S, Piccardo A, Conte M, et al. 131 I-Meta-iodobenzylguanidine followed by busulfan and melphalan and autologous stem cell rescue in high-risk neuroblastoma. Pediatr Blood Cancer. Feb 2021; 68(2): e28775. PMID 33099289
32. Sung KW, Ahn HS, Cho B, et al. Efficacy of tandem high-dose chemotherapy and autologous stem cell rescue in patients over 1 year of age with stage 4 neuroblastoma: the Korean Society of Pediatric Hematology-Oncology experience over 6 years (2000-2005). J Korean Med Sci. May 2010; 25(5): 691-7. PMID 20436703
33. Ladenstein R, Potschger U, Hartman O, et al. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures. Bone Marrow Transplant. Jun 2008; 41 Suppl 2: S118-27. PMID 18545256
34. George RE, Li S, Medeiros-Nancarrow C, et al. High-risk neuroblastoma treated with tandem autologous peripheral-blood stem cell-supported transplantation: long-term survival update. J Clin Oncol. Jun 20 2006; 24(18): 2891-6. PMID 16782928
35. Kletzel M, Katzenstein HM, Haut PR, et al. Treatment of high-risk neuroblastoma with triple-tandem high-dose therapy and stem-cell rescue: results of the Chicago Pilot II Study. J Clin Oncol. May 01 2002; 20(9): 2284-92. PMID 11980999

36. Grupp SA, Stern JW, Bunin N, et al. Rapid-sequence tandem transplant for children with high-risk neuroblastoma. Med Pediatr Oncol. Dec 2000; 35(6): 696-700. PMID 11107149
37. Pasqualini C, Dufour C, Goma G, et al. Tandem high-dose chemotherapy with thiotepa and busulfan-melphalan and autologous stem cell transplantation in very high-risk neuroblastoma patients. Bone Marrow Transplant. Feb 2016; 51(2): 227-31. PMID 26524264
38. Kim EK, Kang HJ, Park JA, et al. Retrospective analysis of peripheral blood stem cell transplantation for the treatment of high-risk neuroblastoma. J Korean Med Sci. Sep 2007; 22 Suppl: S66-72. PMID 17923758
39. Marcus KJ, Shamberger R, Litman H, et al. Primary tumor control in patients with stage 3/4 unfavorable neuroblastoma treated with tandem double autologous stem cell transplants. J Pediatr Hematol Oncol. Dec 2003; 25(12): 934-40. PMID 14663275
40. von Allmen D, Grupp S, Diller L, et al. Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. J Pediatr Surg. Jun 2005; 40(6): 936-41; discussion 941. PMID 15991174
41. Meyers PA. High-dose therapy with autologous stem cell rescue for pediatric sarcomas. Curr Opin Oncol. Mar 2004; 16(2): 120-5. PMID 15075902
42. Meyers PA, Krailo MD, Ladanyi M, et al. High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. J Clin Oncol. Jun 01 2001; 19(11): 2812-20. PMID 11387352
43. Gardner SL, Carreras J, Boudreau C, et al. Myeloablative therapy with autologous stem cell rescue for patients with Ewing sarcoma. Bone Marrow Transplant. May 2008; 41(10): 867-72. PMID 18246113
44. Ladenstein R, Potschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol. Jul 10 2010; 28(20): 3284-91. PMID 20547982
45. Loschi S, Dufour C, Oberlin O, et al. Tandem high-dose chemotherapy strategy as first-line treatment of primary disseminated multifocal Ewing sarcomas in children, adolescents and young adults. Bone Marrow Transplant. Aug 2015; 50(8): 1083-8. PMID 26030048
46. Weigel BJ, Breitfeld PP, Hawkins D, et al. Role of high-dose chemotherapy with hematopoietic stem cell rescue in the treatment of metastatic or recurrent rhabdomyosarcoma. J Pediatr Hematol Oncol. Jun-Jul 2001; 23(5): 272-6. PMID 11464981

47. McDowell HP, Foot AB, Ellershaw C, et al. Outcomes in paediatric metastatic rhabdomyosarcoma: results of The International Society of Paediatric Oncology (SIOP) study MMT-98. Eur J Cancer. Jun 2010; 46(9): 1588-95. PMID 20338746
48. Klingebiel T, Boos J, Beske F, et al. Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. Pediatr Blood Cancer. Apr 2008; 50(4): 739-45. PMID 18286501
49. Carli M, Colombatti R, Oberlin O, et al. High-dose melphalan with autologous stem-cell rescue in metastatic rhabdomyosarcoma. J Clin Oncol. Sep 1999; 17(9): 2796-803. PMID 10561355
50. Presson A, Moore TB, Kempert P. Efficacy of high-dose chemotherapy and autologous stem cell transplant for recurrent Wilms' tumor: a meta-analysis. J Pediatr Hematol Oncol. Aug 2010; 32(6): 454-61. PMID 20505538
51. Garaventa A, Hartmann O, Bernard JL, et al. Autologous bone marrow transplantation for pediatric Wilms' tumor: the experience of the European Bone Marrow Transplantation Solid Tumor Registry. Med Pediatr Oncol. 1994; 22(1): 11-4. PMID 8232074
52. Kremens B, Gruhn B, Klingebiel T, et al. High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. Bone Marrow Transplant. Dec 2002; 30(12): 893-8. PMID 12476282
53. Kullendorff CM, Bekassy AN. Salvage treatment of relapsing Wilms' tumour by autologous bone marrow transplantation. Eur J Pediatr Surg. Jun 1997; 7(3): 177-9. PMID 9241510
54. Pein F, Michon J, Valteau-Couanet D, et al. High-dose melphalan, etoposide, and carboplatin followed by autologous stem-cell rescue in pediatric high-risk recurrent Wilms' tumor: a French Society of Pediatric Oncology study. J Clin Oncol. Oct 1998; 16(10): 3295-301. PMID 9779704
55. Spreafico F, Bisogno G, Collini P, et al. Treatment of high-risk relapsed Wilms tumor with dose-intensive chemotherapy, marrow-ablative chemotherapy, and autologous hematopoietic stem cell support: experience by the Italian Association of Pediatric Hematology and Oncology. Pediatr Blood Cancer. Jul 2008; 51(1): 23-8. PMID 18293386
56. Malogolowkin MH, Hemmer MT, Le-Rademacher J, et al. Outcomes following autologous hematopoietic stem cell transplant for patients with relapsed Wilms' tumor: a CIBMTR retrospective analysis. Bone Marrow Transplant. Nov 2017; 52(11): 1549-1555. PMID 28869618
57. Venkatramani R, Murray J, Helman L, et al. Risk-Based Therapy for Localized Osteosarcoma. Pediatr Blood Cancer. Mar 2016; 63(3): 412-7. PMID 26501936

58. Hong CR, Kang HJ, Kim MS, et al. High-dose chemotherapy and autologous stem cell transplantation with melphalan, etoposide and carboplatin for high-risk osteosarcoma. Bone Marrow Transplant. Oct 2015; 50(10): 1375-8. PMID 26098952
59. Fagioli F, Aglietta M, Tienghi A, et al. High-dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian sarcoma group study. J Clin Oncol. Apr 15 2002; 20(8): 2150-6. PMID 11956277
60. Uemura S, Mori T, Ishiko S, et al. Retrospective analysis of high-dose chemotherapy followed by autologous stem cell transplantation for high-risk pediatric osteosarcoma. Pediatr Hematol Oncol. May 2020; 37(4): 337-343. PMID 32151185
61. Dunkel IJ, Aledo A, Kernan NA, et al. Successful treatment of metastatic retinoblastoma. Cancer. Nov 15 2000; 89(10): 2117-21. PMID 11066053
62. Kremens B, Wieland R, Reinhard H, et al. High-dose chemotherapy with autologous stem cell rescue in children with retinoblastoma. Bone Marrow Transplant. Feb 2003; 31(4): 281-4. PMID 12621463
63. Matsubara H, Makimoto A, Higa T, et al. A multidisciplinary treatment strategy that includes high-dose chemotherapy for metastatic retinoblastoma without CNS involvement. Bone Marrow Transplant. Apr 2005; 35(8): 763-6. PMID 15750608
64. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of metastatic retinoblastoma. Ophthalmology. Jun 2003; 110(6): 1237-40. PMID 12799253
65. Dunkel IJ, Khakoo Y, Kernan NA, et al. Intensive multimodality therapy for patients with stage 4a metastatic retinoblastoma. Pediatr Blood Cancer. Jul 15 2010; 55(1): 55-9. PMID 20486171
66. Ratko TA, Belinson SE, Brown HM, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population (Report No. 12-EHC018-EF). Rockville, MD: Agency for Healthcare Research and Quality; 2012.
67. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Nov 2015; 21(11): 1863-1869. PMID 26256941
68. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bone Cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf.
69. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.

Policy # 00064
Original Effective Date: 01/28/2002
Current Effective Date: 08/09/2021

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
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.

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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.
07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2022

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 2020 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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intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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, C49.0-C49.9, C64.1-C64.9, C69.20-C69.22, C74.00-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. Food and Drug Administration (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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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.