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MEDICAL POLICY – 8.01.511

Hematopoietic Cell Transplantation for Solid Tumors of Childhood

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Effective Date:	Apr. 1, 2025	RELATED MEDICAL POLICIES:	
Last Revised:	Mar. 10, 2025	8.01.28	Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma
Replaces:	8.01.34		

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RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

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

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

Policy Coverage Criteria

Service	Medical Necessity
Autologous hematopoietic cell transplantation	**Autologous hematopoietic cell transplantation may be considered medically necessary for:** • Initial treatment of high-risk neuroblastoma • Recurrent or refractory neuroblastoma • Initial treatment of high-risk Ewing sarcoma • Recurrent or refractory Ewing sarcoma • Metastatic Retinoblastoma
Tandem autologous hematopoietic cell transplantation	**Tandem autologous hematopoietic cell transplantation is considered medically necessary for high-risk, refractory or relapsed neuroblastoma.**

Service	Investigational
Autologous hematopoietic cell transplantation	**Autologous hematopoietic cell transplantation is considered investigational as initial treatment of low- or intermediate-risk neuroblastoma, initial treatment of low- or intermediate-risk Ewing sarcoma, and for other solid tumors of childhood including, but not limited, to the following:** • Retinoblastoma without metastasis • Rhabdomyosarcoma • Osteosarcoma • Wilms Tumors
High-dose chemotherapy autologous cell support	**High-dose chemotherapy (with or without associated radiotherapy) and autologous cell support may be considered investigational for treatment of recurrent Wilms tumor**
Tandem autologous hematopoietic cell transplantation	**Tandem autologous hematopoietic cell transplantation is considered investigational for treatment of all other types of pediatric solid tumors.**
Allogeneic hematopoietic cell transplantation	**Allogeneic (myeloablative or nonmyeloablative) hematopoietic cell transplantation is considered investigational for treatment of pediatric solid tumors.**

Service	Investigational
Salvage allogeneic hematopoietic cell transplantation	**Salvage allogeneic hematopoietic cell transplantation for pediatric solid tumors that relapse after autologous transplant or fail to respond is considered investigational.**

Documentation Requirements

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

For autologous hematopoietic cell transplantation

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

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

For tandem autologous hematopoietic cell transplantation

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

Coding

Code	Description
CPT	
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: phoresis

Code	Description
	and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

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

Related Information

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

Definition of Terms

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

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

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

RIC: This refers to reduced intensity conditioning.

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

Tandem transplantation: This is defined as a HCT technique where the preplanned intent for therapy involves two sequential HCTs. These may be autologous followed by a second autologous (auto-auto) transplantation, autologous followed by allogeneic (auto-allo)

transplantation, or autologous followed by RIC-allogeneic (auto–RIC-allo) transplantation. The "tandem" implies a very short, preplanned interval between the two transplants, as well as the therapeutic intent to do two transplants from the outset of therapy.

Benefit Application

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).
- Some plans may participate in voluntary programs offering coverage for individuals participating in National Institutes of Health-approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.
- Some contracts or certificates of coverage may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

Evidence Review

Description

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

Background

Solid Tumors of Childhood

Solid tumors of childhood arise from mesodermal, ectodermal, and endodermal cells of origin.[1] Some common solid tumors of childhood are neuroblastoma, Ewing sarcoma/Ewing sarcoma family of tumors (ESFT), Wilms tumor, rhabdomyosarcoma (RMS), osteosarcoma, and retinoblastoma.

General Treatment

The prognosis for pediatric solid tumors has improved more recently, mostly due to the application of multiagent chemotherapy and improvements in local control therapy (including aggressive surgery and advancements in radiation therapy).[2] However, individuals with metastatic, refractory, or recurrent disease continue to have poor prognoses, and these "high-risk" individuals are candidates for more aggressive therapy, including autologous 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,[1] with approximately 90% of the cases presenting in children younger than five 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.

Individuals with neuroblastoma are stratified into prognostic risk groups (low, intermediate, and high) that determine treatment plans. Risk variables include age at diagnosis, clinical stage of disease, tumor histology, and certain molecular characteristics, including the presence of the MYCN oncogene. Tumor histology is categorized as favorable or unfavorable, according to the degree of tumor differentiation, the proportion of tumor stromal component, and index of cellular proliferation.[3] It is well established that MYCN amplification is associated with rapid tumor progression and a poor prognosis,[4] even in the setting of other coexisting favorable factors. Loss of heterozygosity (LOH) at chromosome arms 1p and 11q frequently occurs in neuroblastoma.[5] Although 1p LOH is associated with MYCN amplification, 11q is usually found in tumors without this abnormality.[5] Some studies have shown that 1p LOH and unbalanced 11q

LOH are strongly associated with outcome in individuals with neuroblastoma, and both are independently predictive of worse progression-free survival (PFS) in individuals with low- and intermediate-risk disease.[3] Although the use of these LOH markers in assigning treatment in individuals is evolving, they may prove useful to stratify treatment.

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

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 individuals younger than one year of age with stage 1, 2, or 4S with favorable histopathologic findings and no MYCN oncogene amplification. High-risk neuroblastoma is characterized by an age older than 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 as follows:[6]

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 individuals with low-stage disease have excellent outcomes with minimal therapy, and with International Neuroblastoma Staging System stage 1 disease, most individuals can be treated by surgery alone.[7] Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.[7]

For intermediate-risk disease, moderately intensive multiagent chemotherapy is the mainstay of therapy.[8] Surgery is needed to obtain a diagnosis, and the extent of resection necessary to obtain an optimal outcome is not established.[9] Individuals 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.[10]

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

Ewing Sarcoma Family of Tumors

ESFT encompasses a group of tumors that that share some degree of neuroglial differentiation and a characteristic underlying molecular pathogenesis (chromosomal translocation).[11] 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%).[12] These fusion products function as oncogenic aberrant transcription factors. Detection of these fusions is considered to be specific for the ESFT and helps further validate the diagnosis. Included in ESFT are "classic" Ewing's sarcoma of bone, extra-osseous Ewing's, peripheral primitive neuroectodermal tumor (pPNET), and Askin tumors (chest wall).

Most commonly diagnosed in adolescence, ESFT can be found in bone (most commonly) or soft tissue; however, the spectrum of ESFT has also been described in various organ systems. Ewing is the second most common primary malignant bone tumor.[13] 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 the progression-free survival rates in individuals with localized disease to 60–70%.[14] The

presence of metastatic disease is the most unfavorable prognostic feature, and the outcome for individuals presenting with metastatic disease is poor, with 20–30% progression-free survival. Other adverse prognostic factors that may categorize an individual as having "high-risk" Ewing are tumor location (e.g., individuals with pelvic primaries have worse outcomes), larger tumor size, and older age of the individual. However, "high-risk" Ewing has not always been consistently defined in the literature.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma of childhood, shows skeletal muscle differentiation. The most common primary sites are the head and neck (e.g., parameningeal, orbital, pharyngeal), genitourinary tract, and extremities.[15]

Treatment

Specific treatment is based on tumor location, resection, and node status, and may involve surgery, radiotherapy, and chemotherapy.[16] Five-year survival rates for rhabdomyosarcoma increased between 1975 and 2017 from 53% to 71% in children younger than 15 years and from 30% to 52% in 15- to 19-year-olds.[15]

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.[17,18] Similarly, post-relapse mortality is very high. The prognosis of metastatic disease is affected by tumor histology, age at diagnosis, the site of metastatic disease, and the number of metastatic sites.[15]

Wilms Tumor

Wilms tumor is the most common primary malignant renal tumor of childhood.[19] In the US, Wilms tumor is staged using the National Wilms Tumor Study system, which is based on surgical evaluation before chemotherapy as shown below.[20]

Stage	Description
I	(a) Tumor is limited to the kidney and completely excised;

Stage	Description
	(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).[20]

Treatment

In the US, 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 (e.g., 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%.[21] Between 10% and 15% of individuals with favorable histology and 50% of individuals with anaplastic tumors, experience tumor progression or relapse.[21]

Similar risk-adapted strategies are being tested for the 15% of individuals who experience a relapse. Success rates after relapse range from 25% to 45%. For individuals 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%.[22]

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.[23] 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.[24]

The prognosis of osteosarcoma has greatly improved, with 5-year survival rates increasing between 1975 and 2020 from 40% to 72% in children younger than 15 years and from 56% to 71% in 15- to 19-year-olds.[24] Prognostic factors for individuals 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 individuals with recurrent osteosarcoma, the most important prognostic factor is surgical respectability. There is a 5-year survival rate of 20% to 45% in individuals who had a complete resection of metastatic pulmonary tumors and a 20% survival rate for individuals with metastatic tumors at other sites.[24]

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.[25] Cases may be unilateral or bilateral, with bilateral tumor almost always occurring in the heritable type.

Treatment

Treatment options depend on the extent of disease. Retinoblastoma is usually confined to the eye, and with current therapy has a high cure rate. However, once disease spreads beyond the eye, survival rates drop significantly; 5-year disease-free survival is reported to be less than 10% in those with extraocular disease, and stage 4B disease (i.e., disease metastatic to the central nervous system) has been lethal in virtually all cases reported.[26]

The strategy for nonmetastatic disease depends on the disease extent but may include focal therapies (e.g., laser photocoagulation, cryotherapy, plaque radiotherapy), intravitreal chemotherapy, intra-arterial chemotherapy, systemic chemotherapy, enucleation, or a

combination.[27] For metastatic disease, intensive multimodal therapy with high-dose chemotherapy, with or without radiotherapy, is standard care.

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

Hematopoietic Cell Transplantation

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

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and individual 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 individual at all or most human leukocyte antigens loci.

Summary of Evidence

For individuals who have high-risk or relapsed peripheral neuroblastoma who receive single or tandem autologous HCT, the evidence includes randomized controlled trials (RCTs), systematic reviews with meta-analyses of those trials, and observational studies. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. In the pooled analysis, individuals 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, nonrandomized comparative studies, single-arm studies, and case series evaluating tandem autologous HCT showed improvements in

EFS for children with high-risk neuroblastoma. A recent RCT found that tandem autologous HCT resulted in statistically significantly better EFS compared with single HCT. 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 an RCT, single-arm studies, and case series. The 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. An RCT comparing consolidation with HDC plus autologous HCT to standard chemotherapy plus whole lung irradiation in individuals with Ewing sarcoma with pulmonary and/or pleural metastases did not find a significant improvement in EFS in the group that received HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have rhabdomyosarcoma (RMS) who receive single autologous HCT, the evidence includes a systematic review and nonrandomized comparative studies. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Available studies have not demonstrated improvements in overall survival or event-free survival with autologous HCT. Additional research is needed to demonstrate a benefit with autologous HCT for pediatric rhabdomyosarcoma. The evidence is insufficient to determine 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 retrospective studies and a meta-analysis. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Overall four-year survival rates were similar between individuals receiving HCT and receiving chemotherapy. There was a trend suggesting that individuals 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 series and a prospective single-arm study, and a retrospective study. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. An interim analysis of the prospective single-arm study showed that individuals receiving autologous HCT were experiencing lower event-free survival rates than historical controls, resulting in all individuals being enrolled in standard of care chemotherapy. Conversely, a retrospective study found favorable event-free survival and overall survival rates with HDC plus autologous HCT in individuals with nonmetastatic osteosarcoma with low-degree necrosis after

neoadjuvant chemotherapy. 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 localized retinoblastoma who receive single autologous HCT, the evidence includes no studies. The relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The evidence is insufficient to determine 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, case reports, and prospective and retrospective studies. The 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 individuals 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 sufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in **Table 1**.

Table 1. 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	Dec 2024
NCT01505569	Alkylator-Intense Conditioning Followed by Autologous Transplantation for Patients With High Risk or Relapsed Solid or CNS Tumors	44	Feb 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
Peripheral Neuroblastoma			
NCT01526603	High Dose Chemotherapy and Autologous Peripheral Blood Stem Cell (PBSC) Rescue for Neuroblastoma: Standard of Care Considerations	13	May 2023
NCT02605421	Tandem Myeloablative Consolidation Therapy and Autologous Stem Cell Rescue for High-Risk Neuroblastoma	12	Dec 2025
NCT01704716	High Risk Neuroblastoma Study 1 of SIOP-Europe (SIOPEN)	3300	Sep 2026
NCT06172296	A Phase 3 Study of Dinutuximab Added to Intensive Multimodal Therapy for Children With Newly Diagnosed High-Risk Neuroblastoma	485	Dec 2029
Ewing Sarcoma			
NCT03011528	CombinaiR3 - First-line Treatment of Ewing Tumours with Primary Extrapulmonary Dissemination in Patients from 2 to 50 Years	45	Nov 2023

NCT: national clinical trial.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

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

2017 Input

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

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.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy published consensus guidelines for clinically appropriate indications for HCT based on best prevailing evidence.[79] Indications for HCT in pediatric patients with the solid tumor types addressed in this policy are outlined in **Table 2**.

Table 2. 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 Kanate et al (2020).[78]
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 (e.g., 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/immune effector cell therapy (IECT) 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/IECT 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/IECT to be a promising treatment option. HCT/IECT 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): HCT/IECTis not currently recommended for these indications where evidence do not support the routine use of HCT/IECT. However, this recommendation does not preclude investigation of HCT/IECT as a potential treatment and may be pursued for these indications within the context of a clinical trial.

[b] Tandem autologous HCT recommended.

National Comprehensive Cancer Network

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

Table 3. NCCN Guidelines

Guideline	Tumor Type	Year	NCCN Comments
Bone cancer[79]	Osteosarcoma	v1.2024	"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[79]	Ewing sarcoma	v1.2025	"High dose chemotherapy followed by stem cell transplant (HDT/SCT) has been evaluated in patients with localized as well as metastatic disease. HDT/SCT has been associated with potential survival benefit in patients with non-metastatic disease. However, studies that have evaluated HDT/SCT in patients with primary metastatic disease have shown conflicting results…. HDT/SCT has been associated with improved long-term survival in patients with relapsed or progressive Ewing sarcoma in small, single-institution studies. The role of this approach is yet to be determined in prospective randomized studies."
Soft tissue sarcoma[80]	Rhabdomyosarcoma	V4.2024	HCT not addressed
Wilms tumor (nephroblastoma)[81]	Wilms tumor	V2.2024	HCT not addressed

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

National Ewing Sarcoma Tumor Board

The National Ewing Sarcoma Tumor Board published consensus recommendations for systemic therapies in the management of relapsed Ewing sarcoma.[83,] Regarding HCT, the board states that "high-dose therapy with autologous stemcell rescue (HDT) has been attempted for the treatment of patients with ES, in both the upfront and relapsed settings. Although HDT has been

incorporated into the treatment of patients with high-risk neuroblastoma and high-risk medulloblastoma, its role in the treatment of patients with ES remains controversial".

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

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

References

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History

Date	Comments
11/16/00	Add to Therapy Section - New Policy
12/21/00	Replace Policy - Additional minor changes recommended by Oncology Committee
12/10/02	Replace Policy - Policy reviewed; no criteria changes.
06/17/03	Replace Policy - Update CPT codes only.
08/12/03	Replace Policy - Policy updated; no criteria changes. Additional rationale language and references added.
09/01/04	Replace Policy - Policy renumbered from PR.8.01.111. No changes to dates.
12/14//04	Replace Policy - Scheduled review; codes updated; no criteria changes. Approved by OAP 10/29/04.
11/11/05	Replace Policy - Scheduled review; rationale and references updated; no change to policy statement. Recommended by OAP 10/27/05.
06/02/06	Disclaimer and Scope update - No other changes.

Date	Comments
11/14/06	Replace Policy - Policy updated with literature search; no change in policy statement.
12/11/07	Replace Policy - Policy updated with literature review. Policy statement updated to include High-dose chemotherapy and hematopoietic stem-cell support is considered investigational as initial treatment of low- or intermediate-risk neuroblastoma. Multiple cycle high-dose chemotherapy and hematopoietic stem-cell support (i.e., tandem or multiple transplants) is considered investigational for treatment of neuroblastoma. References added. Recommended and reviewed by OAP 11/15/07.
12/31/07	Codes Updated - CPT code 86817 removed as directed by RPIW.
06/10/08	Replace Policy - Policy extensively consolidated and rewritten; updated with literature search. References also extensively revised; no changes to policy statements
12/08/09	Replace Policy - Policy updated with literature search; no change to the policy statement. Recommended and reviewed by OAP August 21, 2009. Code 86817 added back to the policy.
02/09/10	Code Update - New 2010 codes added.
06/08/10	Replace Policy - Policy updated with NCCN 2010 Guidelines. No change to policy statement. Reviewed and recommended by OAP Feb 2010.
06/13/11	Replace Policy - Policy presented to OAP for review May 12, 2011. Policy title changed to "Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood" from "HDC with Hematopoietic Stem-Cell Support for Solid Tumors in Childhood." ICD-10 codes added to policy.
01/25/12	Code 38232 added.
02/09/12	CPT code 38204 was removed from the policy.
06/12/12	Replace Policy. Policy updated with literature search. Policy statement changed: Tandem autologous HSCT, previously considered investigational, may now be considered medically necessary for high-risk neuroblastoma.
09/19/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
09/28/12	Update Related Policies – Add 8.01.20-30, 8.01.514 and 8.01.520.
11/15/12	Reviewed and recommended by OAP, November 2012.
02/01/13	Update Related Policies, change title of policy 8.01.21.
02/15/13	Update Related Policies, change title of policy 8.01.30.
03/20/13	The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.
07/24/13	Replace policy. Policy updated with literature review; Rationale reorganized. References updated, added and renumbered. No change in policy statements.
09/30/13	Update Related Policies. Change title to policy 8.01.31.

Date	Comments
10/18/13	Update Related Policies. Change title to policy 8.01.17.
12/06/13	Update Related Policies. Remove 8.01.31 as it was archived.
01/30/14	Update Related Policies. Change title to 8.01.21.
02/27/14	Update Related Policies. Change title to 8.01.30.
03/21/14	Update Related Policies. Remove 8.01.514 as it was deleted.
04/18/14	Update Related Policies. Delete 8.01.20 and replace with 8.01.529.
06/09/14	Annual Review. Policy updated with literature search. Policy statements changed. Retinoblastoma added to the list of conditions for which autologous HSCT is considered medically necessary; treatment of recurrent Wilms tumor with HDC or autologous HSCT and tandem autologous HSCT for high-risk neuroblastoma remain medically necessary, but now much be conducted as part of a clinical trial.
06/24/14	Update Related Policies. Remove 8.01.35, 8.01.42, 8.01.54, then add 8.01.530 and 8.01.532
02/03/15	Update Related Polices. Remove 8.01.23, 8.01.28 and 8.01.30.
06/09/15	Annual Review. Policy updated with literature review; no change in policy statements. Related Policies removed except 7.01.50. ICD-9 and ICD-10 codes removed; these were informational only.
09/30/16	Coding Update. Remove CPT 86817 from coding table near end of policy.
11/04/16	Coding Update. Removed codes that are transplant benefit related.
12/01/16	Annual review, approved November 8, 2016. No changes to policy statement.
08/01/17	Annual Review, approved July 18, 2017. Policy moved into new format. The word stem dropped from the policy title. Retinoblastoma was divided into metastatic retinoblastoma and retinoblastoma without metastases. HCT for metastatic retinoblastoma is now medically necessary. HCT for retinoblastoma without metastases was added as investigational. HCT for late-stage Wilms Tumor previously covered as medically necessary is now investigational based upon input from BC/BS association, guidelines from the American Society for Bone Marrow Transplant, UpToDate review, and weak support for use from a single clinician. Tandem autologous HCT for high risk or relapsed neuroblastoma is now covered as medically necessary based upon BCBS coverage and literature review.
10/01/18	Annual Review, approved September 20, 2018. Policy updated with literature review through November 2017; no references added. Policy statements unchanged.
10/08/18	Minor edit, added Documentation Requirements section.
05/01/19	Annual Review, approved April 2, 2019. Policy updated with literature review through October 2018; reference 55 added. Policy statements unchanged.

Date	Comments
05/01/20	Annual Review, approved April 7, 2020. Policy updated with literature review through November 2019; no references added. Policy statement unchanged.
04/01/21	Annual Review, approved March 23, 2021. Policy updated with literature review through December 7, 2020; references added. Policy statements unchanged.
05/01/21	Update Related Policies. Removed policy 7.01.50 as it was archived.
04/01/22	Annual Review, approved March 8, 2022. Policy updated with literature review through November 29, 2021; references added. Policy statements unchanged.
10/01/22	Coding update. Removed HCPCS code S2140.
04/01/23	Annual Review, approved March 20, 2023. Policy updated with literature review through November 16, 2022; references added. Minor editorial refinement to policy statements; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Annual Review, approved March 25, 2024. Policy updated with literature review through November 30, 2023; no references added. Policy statements unchanged.
04/01/25	Annual Review, approved March 10, 2025. Policy updated with literature review through November 26, 2024; references added. Policy statements unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.