

Regence

Hematopoietic Cell Transplantation for Solid Tumors of Childhood

Effective: December 1, 2025

Next Review: August 2026

Last Review: October 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

Note: This policy addresses only solid tumors of childhood. Solid tumors in adults are considered separately in Transplant, Policy No. [45.27](#). This policy also does not address hematopoietic cell transplantation (HCT) as a treatment of embryonal tumors arising in the central nervous system (cerebral neuroblastoma), tumors derived from glial cells (i.e., astrocytoma, oligodendroglioma, or glioblastoma multiforme), or germ cell tumors which are considered separately in Transplant, Policy Numbers [45.33](#), and [45.38](#), respectively.

- I. **Autologous** hemopoietic cell transplantation may be considered **medically necessary** for any of the following indications (A. - C.):
 - A. Ewing's sarcoma when either of the following are met:
 1. For initial treatment of high-risk Ewing's sarcoma. Individuals may be categorized as "high-risk" if any of the following are present: metastatic

- disease, unfavorable tumor location (e.g., patients with pelvic primaries have worse outcomes), larger tumor size, or older age of the individual; or
2. To consolidate remissions or as a salvage therapy for those with residual, recurrent or refractory Ewing's sarcoma; or
- B. Neuroblastoma when either of the following are met:
 1. For initial treatment of high-risk neuroblastoma. Individuals may be characterized as high-risk if any of the following are present: age older than 1 year, disseminated disease, MYCN oncogene amplification, or unfavorable histopathologic findings; or
 2. Recurrent or refractory neuroblastoma; or
 - C. Wilms tumor, recurrent, high-risk; or
 - D. Metastatic retinoblastoma
- II. **Tandem autologous** hematopoietic cell transplantation may be considered **medically necessary** for high-risk neuroblastoma characterized by any of the following (A. – D.):
- A. Age older than 1 year; or
 - B. Disseminated disease; or
 - C. MYCN oncogene amplification; or
 - D. Unfavorable histopathologic findings.
- III. The following are considered **investigational**:
- A. Autologous hemopoietic cell transplantation for the following indications: Initial treatment of low- or intermediate-risk Ewing's sarcoma; initial treatment of low- or intermediate-risk neuroblastoma; other solid tumors of childhood, including but not limited to the following: a) Osteosarcoma, b) Retinoblastoma without metastasis, c) Rhabdomyosarcoma, d) Wilms tumor, other than recurrent, high-risk.
 - B. Tandem or multiple hematopoietic cell transplantation for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma (Criterion II.)
 - C. Allogeneic (myeloablative or nonmyeloablative) hematopoietic cell transplantation for treatment of all pediatric solid tumors.
 - D. Salvage allogeneic hematopoietic cell transplantation for all pediatric solid tumors that relapse after autologous transplant or fail to respond.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with

drugs that kill cancer cells. Also called intensification therapy and postremission therapy.

- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Ewing's Sarcoma, neuroblastoma, or Wilms tumor: Indicate if high-risk
- Ewing's Sarcoma: Indicate if request is to consolidate remissions or as a salvage therapy for those with residual, recurrent or refractory Ewing's sarcoma
- Neuroblastoma: Indicate if request is for recurrent or refractory neuroblastoma
- Tandem autologous hematopoietic cell transplantation for high-risk neuroblastoma, indicate if any of the following are present:
 - o age older than 1 year,
 - o disseminated disease,
 - o MYCN oncogene amplification,
 - o or unfavorable histopathologic findings.

CROSS REFERENCES

1. [Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant](#), Transplant, Policy No. 45.03
2. [Placental and Umbilical Cord Blood as a Source of Stem Cells](#), Transplant, Policy No. 45.16
3. [Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults](#), Transplant, Policy No. 45.27
4. [Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma](#), Transplant, Policy No. 45.33
5. [Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors](#), Transplant, Policy No. 45.38

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION FOR SOLID TUMORS

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells 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 cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Autologous HCT takes advantage of the steep dose-response relationship observed with many chemotherapeutic agents and allows for escalation of chemotherapy doses above those limited by myeloablation. The use of allogeneic HCT for solid tumors relies on a graft-versus-tumor effect. Allogeneic HCT is uncommonly used in solid tumors, and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

SOLID TUMORS OF CHILDHOOD

Solid tumors of childhood are defined as those not arising from myeloid or lymphoid cells. Some of the most common solid tumors of childhood are neuroblastoma, Ewing’s sarcoma/Ewing’s Sarcoma Family of Tumors, Wilms tumor, rhabdomyosarcoma, osteosarcoma, and retinoblastoma.

The prognosis for pediatric solid tumors has improved over the last two decades, mostly due to the application of multiagent chemotherapy and improvements in local control therapy (including aggressive surgery and advancements in radiation therapy).^[1] However, patients with metastatic, refractory, or recurrent disease continue to have poor prognoses, and these “high-risk” patients are candidates for more aggressive therapy, including autologous HCT, in an effort to improve event-free survival (EFS) and overall survival (OS).

Descriptions of the solid tumors of childhood that are addressed in this policy are as follows:

PERIPHERAL NEUROBLASTOMA

Note: Cerebral neuroblastoma is considered separately in Transplant No. 45.33 related to embryonal tumors.

Neuroblastoma is the most common extracranial solid tumor of childhood^[2], with 90% of cases presenting in children ages 5 or younger.^[3] These tumors originate where sympathetic nervous system tissue is present, within the adrenal medulla or paraspinal sympathetic ganglia. They are remarkable for their broad spectrum of clinical behavior, with some undergoing spontaneous regression, others differentiating into benign tumors, and still others progressing rapidly and resulting in patient death.

Patients with neuroblastoma are stratified into prognostic risk groups (low, intermediate, and high) that determine treatment plans. Risk variables include age at diagnosis, clinical stage of disease, tumor histology, and certain molecular characteristics, including the presence of the MYCN oncogene. Tumor histology is categorized as favorable or unfavorable, according to the degree of tumor differentiation, proportion of tumor stromal component, and index of cellular proliferation.^[4] It is well established that MYCN amplification is associated with rapid tumor progression and a poor prognosis^[5], even in the setting of other coexisting favorable factors. Loss of heterozygosity (LOH) at chromosome arms 1p and 11q occurs frequently in neuroblastoma.^[6] Although 1p LOH is associated with MYCN amplification, 11q is usually found in tumors without this abnormality. Some recent studies have shown that 1p LOH and unbalanced 11q LOH are strongly associated with outcome in patients with neuroblastoma, and both are independently predictive of worse progression-free survival (PFS) in patients with low- and intermediate-risk disease. Although the use of these LOH markers in assigning treatment in patients is evolving, they may prove useful to stratify treatment.

Clinical stage of disease is based on the International Neuroblastoma Staging System (INSS) as follows:

- Stage 1
Localized tumor with complete gross excision, with or without microscopic residual disease; lymph nodes negative for tumor.
- Stage 2A
Localized tumor with incomplete gross excision; lymph nodes negative for tumor.
- Stage 2B
Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor.
- Stage 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.
- Stage 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.
- Stage 4S
Localized primary tumor as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (marrow involvement less than 10%), limited to children younger than 1 year of age.

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

In general, most patients with low-stage disease have excellent outcomes with minimal therapy, and with INSS stage 1 disease, most patients can be treated by surgery alone.^[2] Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.^[2] In contrast, most children older than 1 year with advanced-stage disease die due to progressive disease, despite intensive multimodality therapy^[2], and relapse remains common. Treatment of recurrent disease is determined by the risk group at the time of diagnosis, and the extent of disease and age of the patient at recurrence.

EWING'S SARCOMA AND THE EWING FAMILY OF TUMORS

Ewing's sarcoma family of tumors (ESFT) encompasses a group of tumors that have in common some degree of 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 (E-twenty-

six) family of transcription factors, either FLI1 (90 to 95%) or ERG (5 to 10%). These fusion products function as oncogenic aberrant transcription factors. Detection of these fusions is considered to be specific for the ESFT, and helps further validate the diagnosis. Included in ESFT are “classic” Ewing’s sarcoma of bone, extraosseous Ewing’s, peripheral primitive neuroectodermal tumor (pPNET), and Askin tumors (chest wall).

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

Current therapy for Ewing’s sarcoma favors induction chemotherapy, with local control consisting of surgery and/or radiation (dependent on tumor size and location), followed by adjuvant chemotherapy. Multiagent chemotherapy, surgery, and radiation therapy have improved the PFS in patients with localized disease to 60 to 70%.^[7] The presence of metastatic disease is the most unfavorable prognostic feature, and the outcome for patients presenting with metastatic disease is poor, with 20 to 30% PFS. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing’s are tumor location (e.g., patients with pelvic primaries have worse outcomes), larger tumor size, or older age of the patient. However, “high-risk” Ewing’s has not always been consistently defined in the literature.

RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS) is a soft tissue malignancy of mesenchymal origin. The most common primary sites are the head and neck (e.g., parameningeal, orbital, pharyngeal), genitourinary tract, and extremities.^[8] Most children with RMS present with localized disease, and with conventional multimodal therapy, the cure rate in this group is 70 to 80%.^[9] However, approximately 15% of children present with metastatic disease, and despite the introduction of new drugs and intensified treatment, the five-year survival is 20 to 30% for this “high-risk” group.^[9, 10]

WILMS TUMOR

Wilms tumor, the most common primary malignant renal tumor of childhood, is highly sensitive to chemotherapy and radiation, and current cure rates exceed 85%.^[11] Ten to 15% of patients with favorable histology and 50% of patients with anaplastic tumors experience tumor progression or relapse.^[11] Similar to newly diagnosed Wilms tumor, relapsed Wilms tumor is a heterogeneous disease, and current treatment strategies stratify intensity and scheduling of the treatment modalities based on prognostic features. For newly diagnosed disease, the most important prognostic features are stage and histology. Similar risk-adapted strategies are being attempted for the 15% of patients who experience relapse. Success rates after relapse range from 25 to 45%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse less than 6 to 12 months after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases) event-free survival is less than 15%.^[12] However, recent trials with HDC and autologous HCT have reported three- or four-year OS rates from 60 to 73%.^[13]

OSTEOSARCOMA

Osteosarcoma is a primary malignant bone tumor that is characterized by formation of bone or osteoid by the tumor cells. Osteosarcoma occurs predominantly in the appendicular skeleton of adolescents. In children and adolescents, more than 50% of these tumors arise from bones around the knee. The prognosis of localized osteosarcoma has greatly improved over the last 30 years with OS rates increasing from 10% with surgery alone (usually amputation) to 70% with the introduction of neoadjuvant chemotherapy and limb-sparing surgery.^[14] However, 30 to 40% of patients with non-metastatic osteosarcoma of the extremities experience recurrent disease, most commonly in the lungs.^[14] Mean five-year post-relapse survival rate is approximately 28%, with some groups having a 0% OS rate. Prognostic factors for recurrence include site and size of the primary tumor, presence of metastases at the time of diagnosis, resection adequacy, and tumor response to preoperative chemotherapy (measured as percent of tumor necrosis in the resection specimen). Overall EFS for patients with metastatic disease at diagnosis is about 20 to 30%.^[15]

RETINOBLASTOMA

Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (25 to 30%) or nonheritable (70 to 75%) tumor.^[16] Cases may be unilateral or bilateral, with bilateral tumors almost always occurring in the heritable type. The type of treatment depends on the extent of disease. Retinoblastoma is usually confined to the eye, and with current therapy, has a high cure rate. However, once disease has spread beyond the eye, survival rates drop significantly; five-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 CNS) has been lethal in virtually all cases reported.^[17]

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.^[18] For metastatic disease, intensive multimodal therapy with high-dose chemotherapy, with or without radiotherapy, is standard care.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of pediatric solid tumors are typically measured in units of survival past treatment: event-free survival (EFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of peripheral neuroblastoma, Ewing's sarcoma, or any other solid childhood malignancy, clinical trials that compare this therapy with standard medical treatment (chemotherapy, and/or surgical resection with or without radiation), are needed. Further, for treatment of malignant solid tumors, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

PERIPHERAL NEUROBLASTOMA

Single Autologous Hematopoietic Cell Transplantation (HCT)

Systematic Review

Zebrowska (2024) published a systematic literature review to compare survival outcomes in patients with newly diagnosed high-risk neuroblastoma who were treated with or without myeloablative therapy (MAT) and autologous stem cell transplant (ASCT) and with or without anti-disialoganglioside 2 (GD2) maintenance therapy after ASCT.^[19] The review included 41 publications reporting 34 comparative studies. Seven publications reported four RCTs. Meta-analysis of the RCTs found that event-free survival (EFS) was improved with MAT+ASCT compared to conventional chemotherapy or no further treatment ($p=0.001$). OS was also improved with MAT+ASCT but the difference was not significant ($p=0.05$). The greatest benefit was associated with MAT+ASCT after incomplete surgical resection compared to no MAT+ASCT at 10 years (85% vs. 25%, $p=0.015$). The authors state the anti-GD2 after induction therapy and without MAT+ASCT has been proposed. The analysis of MAT+ASCT followed by anti-GD2 compared to anti-GD2 therapy alone was limited due to lack of comparative studies, but the available evidence suggests an increased risk for relapse in the absence of MAT-ASCT. The review was limited by high heterogeneity, especially in the non-randomized studies. The authors conclude that MAT+ASCT reduces the risk of relapse of high-risk neuroblastoma and should remain the standard of care.

In 2013, Yalcin published a Cochrane meta-analysis on the three well-designed, randomized controlled trials (RCTs)^[20-23] using autologous hematopoietic cell transplantation (HCT) in the treatment of 739 children with high-risk neuroblastoma.^[24] The primary objective was to compare the efficacy of myeloablative therapy with conventional therapy. The included studies all used an age of one year as the cut-off point for pretreatment risk stratification. There was a statistically significant difference in EFS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (three studies, 739 patients; hazard ratio [HR]=0.78, 95% CI 0.67 to 0.90). There was a statistically significant difference in OS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (two studies, 360 patients; HR=0.74, 95% CI 0.57 to 0.98). However, when additional follow-up data were included in the analyses, the difference in EFS remained statistically significant (three studies, 739 patients; HR=0.79, 95% CI 0.70 to 0.90), but the difference in OS was no longer statistically significant (two studies, 360 patients; HR=0.86, 95% CI 0.73 to 1.01). The meta-analysis of secondary malignant disease and treatment-related death did not show any statistically significant differences between the treatment groups. Data from one study (379 patients) showed a significantly higher incidence of renal effects, interstitial pneumonitis, and veno-occlusive disease in the myeloablative group compared with conventional chemotherapy, whereas for serious infections and sepsis, no significant difference between the treatment groups was identified. No information on quality of life was reported.

Available evidence on the use of autologous HCT in high-risk neuroblastoma is sufficient to suggest treatment benefit with transplant.

Tandem Hematopoietic Cell Transplantation (HCT)

Systematic Review

A comparative effectiveness review was conducted on the use of hematopoietic cell transplantation in the pediatric population by the Blue Cross and Blue Shield Association Technology Evaluation Center for the Agency for Healthcare Research and Quality (AHRQ).^[25] The review concluded that the body of evidence on overall survival with tandem HCT

compared to single HCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.

Randomized Controlled Trials

Park (2019) reported results of an RCT that compared tandem autologous transplant to single transplant in high-risk neuroblastoma patients.^[26] Patients were enrolled from 2007 to 2012 at 142 Children's Oncology Group centers. Of the 652 patients enrolled, 270 were excluded due to patient choice or ineligibility and 355 were randomized 1:1 to receive tandem transplant (n = 176) or single transplant (n = 179). The primary outcome was EFS, reported as time from randomization to the occurrence of the first event (relapse, progression, secondary malignancy, or death from any cause). The median follow-up for patients without an event was 5.6 (0.6 to 8.9) years. Of the randomized patients, 83.7% completed the study and 5.9% were lost to follow-up after receiving therapy. The three-year EFS was 61.6% (95% confidence interval (CI), 54.3 to 68.9%) in the tandem transplant group and 48.4% (95% CI 41.0 to 55.7%) in the single transplant group (one-sided log-rank p=0.006). A post-hoc analysis found no difference in three-year OS between the groups. During consolidation therapy, the two most commonly reported grade 3 or higher toxicities were mucosal (12.9%) and infections (17.4%) toxicities. There were 17 deaths due to toxicity during the induction and consolidation therapies combined. One limitation of this study is the large proportion of non-randomized patients, due in large part to parent or physician preference, which may lead to selection bias.

Nonrandomized Studies

Sung (2010) retrospectively analyzed the efficacy of single versus tandem autologous HCT in patients older than one year of age newly diagnosed with stage 4 neuroblastoma from 2000 to 2005 who were enrolled in the Korean Society of Pediatric Hematology-Oncology registry.^[27] Patients were assigned to receive a single (n=70) or tandem (n=71) autologous HCT at diagnosis; 57 and 59 patients underwent single and tandem transplantation as scheduled, respectively. Patient characteristics between the two groups were similar with the exception of a higher proportion of patients in the tandem group having bone metastases. Median follow-up was 56 months (range 24-88 months) from diagnosis. Transplant-related mortality occurred in nine patients in the single transplant group and in eight in the tandem group (two after the first transplant and six after the second). The intent-to treat survival rate was five-year EFS for single versus tandem 31.3% +/- 11.5% and 51.2% +/- 12.4%, respectively; p=0.03. When the survival analysis was confined to the patients who proceeded to transplant, the probability of relapse-free survival (RFS) after the first transplant was higher in the tandem group than the single group with borderline significance (59.1% +/- 13.5% vs. 41.6% +/- 14.5%; p=0.099). The difference became significant when the analysis was confined to patients who did not achieve a CR prior to the first transplant (55.7% +/-17.0% vs. 0%; p=0.012). The authors concluded that tandem HCT for high-risk neuroblastoma is superior to single HCT in terms of survival, particularly in patients not in CR prior to the HCT.

Ladenstein (2008) reported on 28 years of experience for more than 4,000 transplants for primary (89%) and relapsed (11%) neuroblastoma in the European Group for Blood and Marrow Transplantation registry.^[28] Procedures included single autologous (n=2,895), tandem autologous (n=455) and allogeneic HCT (n=71). The median age at the time of transplantation was 3.9 years (range 0.3 to 62 years), with 77 patients older than 18 years. The median follow-up time from HCT was 9 years. Transplant-related mortality (TRM) decreased over time in the registry for the patients who received autologous transplants only. The cumulative incidence of

TRM was 4%, 6%, and 8%, respectively, at day 100, one year, and five years for the autologous group, and 13%, 16%, and 18%, respectively for the allogeneic group. Five-year OS for the autologous group (single and tandem) was 37% versus 25% in the allogeneic setting. Five-year OS for single versus tandem autologous HCT was 38% versus 33%, respectively ($p=0.105$).

Kim (2007) reported a retrospective analysis of 36 patients with high-risk (stage 3 or 4) neuroblastoma who underwent either a single autologous HCT ($n=27$) or a tandem autologous HCT ($n=9$) at Seoul National University Children's Hospital between 1996 and 2004.^[29] EFS of patients who underwent double HCT was similar to that of patients who underwent a single autologous HCT ($p=0.5$).

George (2006) reported long-term survival data of high-risk neuroblastoma patients ($n=82$) treated with tandem autologous HCT between 1994 and 2002.^[30] Median age at diagnosis was 35 months (range 6 months to 18 years). Three- and five-year OS were 74% (95% CI 62 to 82%) and 64 % (95% CI 52 to 74%) respectively.

von Allmen (2005) reported outcomes on 76 patients with previously untreated high-risk stage III/IV neuroblastoma treated with aggressive surgical resection with or without local radiation therapy followed by tandem autologous high-dose chemotherapy and stem-cell rescue.^[31] Overall EFS for the series at three years was 56%.

Marcus (2003) reported outcomes in 52 children with stage 4 or high-risk stage 3 neuroblastoma treated with induction chemotherapy, surgical resection of the tumor when feasible, local radiotherapy and consolidation with tandem autologous HCT.^[32] Radiotherapy was given if gross or microscopic residual disease was present prior to the myeloablative cycles ($n=37$). Of the 52 consecutively treated patients analyzed, 44 underwent both transplants, 6 underwent a single transplant, and 2 progressed during induction. The three-year EFS was 63%, with a median follow-up of 29.5 months.

Kletzel (2002) reported on the outcomes of 25 consecutive newly diagnosed high-risk neuroblastoma patients and one with recurrent disease, diagnosed between 1995 and 2000, and treated with triple-tandem autologous HCT.^[33] After stem-cell rescue, patients were treated with radiation to the primary site. Twenty-two of the 26 patients successfully completed induction therapy and were eligible for the triple-tandem consolidation high-dose therapy. Seventeen patients completed all three cycles of high-dose therapy and stem-cell rescue, two patients completed two cycles and three patients completed one cycle. There was one toxic death, and one patient died from complications of treatment for graft failure. Median follow-up was 38 months, and the three-year EFS and survival rates were 57% $\pm$ 11% and 79% $\pm$ 10%, respectively.

Grupp (2000) reported the outcomes of a Phase II trial that involved 55 children with high-risk neuroblastoma who underwent tandem autologous HCT.^[34] Five patients completed the first HCT course but did not complete the second. There were four toxic deaths. With a median follow-up of 24 months from diagnosis, three-year EFS was 59%.

Despite the low-quality of existing evidence on the use of tandem autologous HCT for treatment of high-risk neuroblastoma, there is a suggestion of potentially increased survival with tandem transplant compared with single transplant.

Reduced Intensity Conditioning

Prete (2024) published a phase II prospective study to determine the effectiveness of reduced-intensity conditioning (RIC) allogeneic HSCT in children with high-risk neuroblastoma and an available HLA-matched donor (related or unrelated).^[35] The study included 51 children aged ≤18 years with:

- High-risk neuroblastoma with planned allogeneic HSCT after initial treatment (n=5)
- Non high-risk neuroblastoma and disease relapse at six months or longer after autologous HSCT (n=2)
- Refractory or relapsed high-risk neuroblastoma (n=44)

Primary study outcomes were cumulative incidence of neutrophil and platelet engraftment, five-year treatment-related mortality (TRM) and disease-free survival (DFS). Secondary outcomes were acute and chronic graft vs. host disease (GVHD). At the time of study publication 46 participants had died, primarily from disease progression. Median follow-up of the five surviving patients is 7.5 years. At 100 days post-HSCT cumulative neutrophil engraftment was 97.9% and platelet engraftment was 93.8%. TRM was 5.9% at 100 days, 17.7% at one year, and 29.4% at five years. There was not a significant difference in 5-year TRM between related and unrelated donor HSCT (p=0.255), or between 9/10 and 10/10 HLA match (p=0.630). Five-year DFS was 14.8% for HSCT from related donor and 8.3% from unrelated donor, which was not significant (p=0.86). However, DFS was longer for participants who had HSCT within 12 months of initial diagnosis (p=0.013) and when bone marrow, not peripheral blood stem cells were used (p<0.001). The incidence of GVHD at 100 days was 41.2% with related donors and 53.5% with unrelated donors, which was not significantly different (p=0.377). The authors concluded that while TRM from RIC allogeneic HSCT was relatively low, the treatment cannot be considered effective due to high rate of disease progression and subsequent 90% overall mortality rate.

Sung (2011) evaluated feasibility and efficacy of reduced-intensity allogeneic cell transplantation (RI alloSCT) in six children with neuroblastoma who failed tandem HDCT/autoSCT.^[36] Although the regimen-related short-term toxicity was manageable in intensively pretreated patients, graft-versus-tumor effect was not sufficiently strong to control tumor progression in patients who had a significant tumor burden at transplant.

EWING SARCOMA AND THE EWING FAMILY OF TUMORS

During the 1980's and 90's, several small series, case reports, and a report from the European Bone Marrow Transplant Registry suggested that autologous HCT could improve the outcome for patients with high-risk ESFT.^[37] The original policy position on Ewing sarcoma was based on these studies and reports. Subsequent to the publication of these reports, additional evidence has been reported on the use of autologous HCT in ESFT, including a systematic review and several non-randomized studies.

Systematic Review

Ramamurthy (2024) published a systematic review that compared outcomes from autologous HSCT (ASCT) in patients with Ewing sarcoma (ES) or rhabdomyosarcoma (RMS) compared to conventional chemotherapy.^[38] In the review 29 of 41 studies were of ASCT for Ewing sarcoma only, and two studies included ASCT treatment for both ES and RMS. For Ewing sarcoma the review found randomized prospective evidence of improved survival with ASCT for high-risk

localized disease. Retrospective evidence suggests improved survival from ASCT for relapsed/refractory ES in selected patients, primarily those in complete or partial remission prior to ASCT. The authors found no proven benefit of improved survival in the treatment of primary localized (not high-risk), metastatic disease, either at initial diagnosis or relapse, or refractory ES. The review of studies addressing RMS is described below.

The AHRQ comparative effectiveness review of HCT in the pediatric population also addressed ESFT, concluding that low-strength evidence on overall survival suggests no benefit with single autologous HCT compared with conventional therapy for the treatment of high-risk ESFT.^[25] The body of evidence on overall survival with tandem autologous HCT compared with single autologous HCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.

Randomized Controlled Trials

Koch (2022) reported results of the Phase III, open-label, prospective, multicenter, randomized controlled Ewing 2008R3 trial.^[39] High-risk Ewing sarcoma patients (n=109) were randomized to receive TreoMel-HDT (treosulfan and melphalan high-dose chemotherapy followed by reinfusion of autologous hematopoietic stem cells) or no further treatment, both following six cycles of vincristine, ifosfamide, doxorubicin, and etoposide induction and eight cycles of vincristine, actinomycin D, and cyclophosphamide consolidation therapy. Median follow-up was 3.3 years. Overall, no statistically significant difference in EFS (the primary end point) was identified between groups (HR 0.85; 95% CI 0.55 to 1.32, intention-to-treat). A subgroup analysis identified a significant difference between groups for EFS in patients under 14 years of age (HR 0.40; 95% CI 0.19 to 0.87; treatment-sex interaction p=0.0159). Significantly more infections, gut and renal toxicities occurred during consolidation therapy in the TreoMel-HDT group (p<0.05).

Nonrandomized Studies

Dirksen (2019) reported results of the R2Pulm open label trial, a component of the European Ewing Tumour Working Initiative of National Groups, 99 Trial (see below) and the Ewing 2008 trial that included Ewing sarcoma patients with isolated pulmonary metastases.^[40] The primary objective in R2Pulm was to evaluate whether consolidation with HDC plus autologous HCT (n=144) improved EFS compared with consolidation with standard chemotherapy plus whole lung irradiation (n=143). No statistically significant difference was identified in EFS between treatment groups. EFS at three and eight years was 56.6% and 52.9% for HDC plus autologous HCT, respectively, and 50.6% and 43.1% for standard chemotherapy plus whole lung irradiation, respectively. Nine patients died in the HDC plus autologous HCT group (six of these deaths were treatment-related and three were either due to secondary malignancy, another cause, or unknown cause), and two died after standard chemotherapy plus whole lung irradiation (one death was treatment-related and one was due to another cause). Severe acute toxicities were also more prevalent in the group who received HDC plus autologous HCT.

In 2015, Jahnukainen reported their single-institution experience with high-dose thiotepa as consolidation therapy with autologous HCT for high-risk Ewing family tumors. Data from 24 patients who were treated between 1986 and 2012 were retrospectively analyzed. Ewing family tumor patients received single and tandem high-dose therapy with special emphasis on HD-thiotepa as the emphasis of the regimen. The 10-year overall survival for the entire cohort was 0.73±0.01. Thirteen out of the 24 underwent high-dose therapy (10 single, 3 tandem). There was no toxic mortality.

Early case series were characterized by small numbers of patients, and comparison of the studies was difficult for several reasons. Within each report, patients often received a variety of chemotherapeutic regimens and many of the studies did not share the same patient eligibility criteria (and in some, the definition of high risk included patients with criteria that did not result in inferior prognosis). In addition, some studies used autologous, and others allogeneic HCT.

Subsequent to the early wave of publications, in 2001, Meyers reported on a prospective study with autologous HCT in 32 patients with newly diagnosed Ewing's sarcoma metastatic to bone and/or bone marrow.^[41] Induction therapy consisted of five cycles of cyclophosphamide-doxorubicin-vincristine, alternating with ifosfamide-etoposide. Twenty-three patients proceeded to the consolidation phase with melphalan, etoposide, total body irradiation, and autologous HCT (of the nine patients who did not proceed, two were secondary to toxicity and four to progressive disease). Three patients died during the high-dose phase. Two-year EFS for all eligible patients was 20% and 24% for the 29 patients who received the high-dose consolidation therapy. The study concluded that consolidation with high-dose chemotherapy (HDC), TBI, and autologous stem-cell support failed to improve the probability of EFS for this cohort of patients when compared with a similar group of patients treated with conventional therapy. The authors noted that their findings differed from some previous studies and noted that the previous studies suffered from heterogeneous patient populations. The authors concluded that future trials of autologous HCT must be conducted prospectively, with identification of a group at high risk for failure, and all patients entering the study at the same point in therapy.

Gardner reported the results of 116 patients with Ewing's sarcoma who underwent autologous HCT (80 as first-line therapy and 36 for recurrent disease) between 1989 and 2000.^[42] Five-year probabilities of PFS in patients who received HCT as first-line therapy were 49% (95% CI 30 to 69%) for those with localized disease at diagnosis and 34% (95% CI 22 to 47%) for those with metastatic disease at diagnosis. For the population with localized disease at diagnosis and recurrent disease, five-year probability of PFS was 14% (95% CI 3 to 30%). The authors concluded that PFS rates after autologous HCT were comparable to rates seen in patients with similar disease characteristics treated with conventional therapy.

Results from one group of patients in the Euro-EWING 99 trial were reported by Ladenstein for patients with primary disseminated multifocal Ewing sarcoma (PDMES).^[43] From 1999 to 2005, 281 patients with PDMES were enrolled in the Euro-EWING 99 R3 study; the Euro-EWING99 Committee agreed to stop enrollment to this group and release the data. Median age was 16.2 years (range: 0.4 to 49 years). Patients with isolated lung metastases were not part of the analysis. The recommended treatment consisted of induction chemotherapy, HDC and autologous HCT and local treatment to the primary tumor (surgery and/or radiation or neither). Induction therapy was completed by 250 (89%) of patients. One-hundred sixty-nine (60%) of the patients proceeded to HCT; reasons for not proceeding to HCT included disease progression or other or unknown reasons. One patient died during induction therapy from sepsis. High-dose chemotherapy TRM consisted of three patients dying within the first 100 days after high-dose therapy- one from acute respiratory distress syndrome and two from severe veno-occlusive disease and septicemia; late deaths included three patients who died 1-1.5 years after high-dose therapy. After a median follow-up of 3.8 years, score allowed allocation of patients with PDMES at diagnosis to three risk groups with the following outcomes: group 1 (score ≤ 3 ; n=82) EFS of 50%, group 2 (score >3 but <5 ; n=102) EFS of 25%, and group 3 (score ≥ 5 ; n=70) EFS of 10% ($p<0.0001$). The authors concluded that this scoring system may facilitate risk-adapted treatment strategies. The estimated three-year EFS

and OS for all 281 patients were 27% +/- 3% and 34% +/- 4%, respectively. Individual risk factors were brought into a scoring model to predict outcome at diagnosis. The values of the score points were based on log-hazard ratios, and the factor with the smallest hazard ratio was assigned one point. One score point was attributed to the following risk factors: age older than 14 years, bone marrow metastases, one bone lesion and additional presence of lung metastases; 1.5 points were attributed to the risk factors of primary tumor volume ≥ 200 mL and more than one bone lesion.

RHABDOMYOSARCOMA

Available evidence on the use of HCT in rhabdomyosarcoma (RMS) consists of several systematic reviews summarizing a body of non-randomized trials.

Systematic Reviews

In addition to the systematic review of ASCT for Ewing sarcoma (ES) described above, the Ramamurthy (2024) review included ten studies that addressed ASCT for RMS, and two studies that evaluated ASCT for both ES and RMS.^[38] Two studies were prospective, and none were RCTs. The authors note that while some studies found evidence of improved EFS and/or OS from ASCT for RMS, the highest quality evidence from two large prospective trials found no benefit in OS or EFS from ASCT for patients with primary metastatic disease. The authors conclude that ASCT for RMS should only be offered within a clinical trial.

A 2010 Cochrane review of non-randomized studies, the effectiveness of HDC with stem cell rescue (SRC) versus standard-dose chemotherapy in improving event-free survival (EFS) and overall survival (OS) of children and young adults with metastatic rhabdomyosarcoma was assessed.^[44] The review concluded that use of HDC with SCR as a standard therapy for children with metastatic rhabdomyosarcoma is not justified at this time. Overall, the quality and quantity of evidence is limited as no RCTs could be identified, and available non-randomized studies have significant methodological limitations, especially selection bias. The review stated that only large, prospective RCTs could answer whether HDC with SCR improves survival in rhabdomyosarcoma.

The AHRQ comparative effectiveness review noted previously also considered the use of HCT in RMS.^[25] The following conclusions were offered:

- Moderate-strength evidence on overall survival suggests no benefit with single HCT compared to conventional therapy for the treatment of high-risk metastatic rhabdomyosarcoma.
- The body of evidence on overall survival with single HCT compared to conventional therapy for the treatment of high-risk rhabdomyosarcoma of mixed tumor type is insufficient to draw conclusions.
- The body of evidence on overall survival with single HCT compared to conventional therapy for the treatment of congenital alveolar rhabdomyosarcoma, cranial paraneurial rhabdomyosarcoma with metastasis, or the use of allogeneic transplantation for metastatic rhabdomyosarcoma was insufficient to draw conclusions.

Weigel published a systematic review on 2001 on the role of autologous HCT in the treatment of metastatic or recurrent rhabdomyosarcoma, which involved a total of 389 patients from 22 studies.^[45] Based on all of the data analyzing EFS and OS, they concluded that there was no significant advantage to undergoing this type of treatment.

Nonrandomized Studies

Autologous HCT has been evaluated in a limited number of patients with “high-risk” RMS (stage 4 or relapsed) in whom complete remission (CR) is achieved after standard induction therapy. Data are relatively scarce, due in part to the rarity of the condition.

Carli conducted a prospective non-randomized study of 52 patients with metastatic RMS, who were in complete remission after induction therapy and subsequently received HDC (“megatherapy”) and autologous HCT and compared them to 44 patients who were in remission after induction therapy who subsequently received conventional chemotherapy.^[46] No significant differences existed between the two study groups (i.e., no differences in clinical characteristics, induction chemotherapy received, sites of primary tumor, histologic subtype, age, or presence/extent of metastases). Three-year EFS and OS were 29.7% and 40%, respectively, for the autologous HCT group and 19.2% and 27.7%, respectively, for the group that received standard consolidation chemotherapy. The difference was not statistically significant ($p=0.3$ and 0.2 for EFS and OS, respectively). The median time after chemotherapy to relapse was 168 days for the autologous HCT group, and 104 days for the standard chemotherapy group ($p=0.05$). Therefore, although there was some delay to relapse, there was no clear survival benefit from using autologous HCT compared to conventional chemotherapy.

Klingebiel prospectively compared the efficacy of two HDC treatments followed by autologous stem-cell rescue versus an oral maintenance treatment (OMT) in 96 children with stage IV soft tissue sarcoma (88 of whom had rhabdomyosarcoma).^[47] Five-year OS probability for the whole group was 0.52 ± 0.14 for the patients who received OMT ($n=51$) and 0.27 ± 0.13 for the transplant group ($n=45$; $p=0.03$). For the patients with rhabdomyosarcoma, five-year OS probability was 0.52 ± 0.16 with OMT versus 0.15 ± 0.12 with transplant ($p=0.001$). The authors concluded that transplant has failed to improve prognosis in metastatic soft tissue sarcoma, but that OMT could be a promising alternative.

McDowell reported the results of the International Society of Paediatric Oncology (SIOP) study MMT-98, for pediatric patients from 48 centers with metastatic rhabdomyosarcoma, entered into the study from 1998 to 2005.^[48] There were a total of 146 patients entered, aged six months to 18 years. The patients were risk-stratified and treated accordingly. One hundred and one patients were considered poor risk patients (PRG) if they were older than 10 years of age, or had bone marrow or bone metastases. Planned therapy for the PRG was induction therapy, sequential high-dose chemotherapy and peripheral blood autologous HCT and finally, maintenance therapy. Seventy-nine of the 101 PRG patients (78.2%) underwent the high-dose therapy, after which 67.1% achieved a partial or complete response. Sixty-seven of the 101 PRG patients received local treatment: 37 radiation alone, 10 surgery alone and 20 both modalities. No treatment-related deaths were reported in the PRG. Three- and five-year EFS for the PRG group was 16.5% and 14.9%, respectively and three- and five-year OS were 23.7% and 17.9%, respectively [$HR=2.46$; CI 1.51 to 4.03; $p<0.001$].

WILMS TUMOR

Most studies of autologous HCT for high-risk Wilms tumor have been very small series or case reports.^[11, 13, 49] A systematic review and meta-analysis have also been published and comprise the focus of this review.

Systematic Reviews

The AHRQ review discussed above also addressed HCT in pediatric patients with Wilms tumor, concluding: Low-strength evidence on overall survival suggests no benefit with single HCT compared to conventional therapy for the treatment of high-risk relapsed Wilms tumor.^[25]

A meta-analysis reported on the efficacy of autologous HCT in recurrent Wilms' tumor for articles published between 1984 and 2008 that reported survival data.^[50] Six studies were included for a total of 100 patients, and patient characteristics and treatment methods were similar across studies, although there was variation in the preparative regimens used.^[11, 13, 49, 51-53] Patients were between the ages of 11 months and 16 years, and had similar primary tumor stage, relapse location and time to relapse across studies. The four-year OS among the 100 patients was 54.1% (42.8 to 64.1%) and four-year EFS based on 79 patients was 50.0% (37.9 to 60.9%). A multivariate analysis found that site of relapse and histology were important predictors for survival, in that patients who did not have a lung-only relapse had more than three times the risk of death or recurrence than patients who relapsed in the lungs only, and the patients with unfavorable histology had more than twice the risk of death compared to those with favorable histology (hazard ratios 3.5 and 2.4, respectively). The authors compared the survival rates from these six studies in which the patients were treated with autologous HCT to patients treated with conventional chemotherapy between 1995 and 2002. The authors found that, in general, the chemotherapy treated patients had comparable or improved four-year survival compared to the HCT group, however, there was a suggestion that patients with lung-only stage 3 and 4 relapse may benefit from autologous HCT with a 21.7% survival advantage over the chemotherapy patients (however the ranges were very wide): four-year OS for the stage 3 and 4 patients with lung only relapse treated with HCT versus chemotherapy was 74.5% (51.7 to 87.7%) and 52.8% (29.7 to 71.5%), respectively.

Nonrandomized Studies

Delafoy (2021) published a retrospective analysis describing the outcomes of 54 patients with Wilms tumor in France who received HDC plus autologous HCT as first-line treatment or following disease recurrence between 2000 and 2016.^[54] The five-year estimates for EFS and OS in patients receiving first-line treatment were 54% (95% CI 32 to 76%) and 62% (95% CI 31 to 82%), respectively. The five-year estimates for EFS and OS in patients receiving treatment following disease recurrence were 57% (95% CI 39 to 71%) and 69% (95% CI 52 to 81%), respectively. Treatment-related death occurred in three patients.

Malogolowkin (2017) published a retrospective analysis describing the outcomes of 253 patients with relapsed Wilms tumor (WT) who received high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplant (HCT) between 1990 and 2013 that were reported to Center for International Blood and Marrow Transplant Research.^[55] The five-year estimates for event-free survival (EFS) and overall survival (OS) were 36% (95% CI 29 to 43%) and 45% (95 CI 38 to 51%), respectively. Relapse of primary disease was the cause of death in 81% of the population. EFS, OS, relapse, and transplant-related mortality showed no significant differences when broken down by disease status at transplant, time from diagnosis to transplant, year of transplant, or conditioning regimen. The data suggest that high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplant (HCT) for relapsed WT is well tolerated and outcomes are similar to those reported in the literature. The greatest limitation of the study is its retrospective, registry-based analyses and that the data originate from basic forms, and thus, did not include histology, site of metastases, stage of disease, genetic syndrome, tumor spillage, and radiation.

OSTEOSARCOMA

Rare small series and case reports are available examining the use of autologous HCT in osteosarcoma.^[56, 57] Autologous HCT has been successful in inducing short-lasting remissions but has not shown an increase in survival.^[14, 58]

RETINOBLASTOMA

Localized Retinoblastoma

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

Metastatic Retinoblastoma

Most studies of autologous HCT for metastatic retinoblastoma have been very small series or case reports.^[59-64] In addition, one systematic review also addresses the use of autologous HCT in retinoblastoma.

Systematic Review

The AHRQ review considered above addressed the use of HCT in pediatric patients with retinoblastoma, concluding that available evidence on overall survival suggests no benefit with single HCT compared to conventional therapy for the treatment of extraocular retinoblastoma with central nervous system involvement.^[25] The body of evidence on overall survival with single HCT compared with conventional therapy for the treatment of extraocular retinoblastoma without central nervous system (CNS) involvement was insufficient to draw conclusions. Likewise, the body of evidence on overall survival with single HCT compared with conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was also insufficient to draw conclusions.

Nonrandomized Studies

Dunkel reported the outcomes of 15 consecutive patients with stage 4a metastatic retinoblastoma who presented between 1993 and 2006 and were treated with HDC and autologous HCT.^[65] Twelve patients had unilateral retinoblastoma and three had bilateral disease. Metastatic disease was not detected at the time of diagnosis, but became clinically evident at a median of six months (range: 1 to 82 months) post-enucleation. The patients had metastatic disease to bone marrow (n=14), bone (n=10), the orbit (n=9) and/or the liver (n=4). Two patients progressed prior to HCT and died. Thirteen patients underwent HCT, and 10 are retinoblastoma-free in first remission at a median follow-up of 103 months (range: 34-202 months). Three patients recurred 14-20 months post-diagnosis of metastatic disease, (two in the CNS and one in the mandible), and all died of their disease. Five-year retinoblastoma-free and event-free survival were 67% (95% CI 38 to 85%) and 59% (31 to 79%), respectively. Six of the 10 patients who survived received radiation therapy. Three patients developed secondary osteosarcoma at 4, 9 and 14 years after diagnosis of metastatic disease, two in previously irradiated fields and one in a non-irradiated field. The authors concluded that HCT was curative for the majority of patients treated in their study with stage 4a retinoblastoma.

Dunkel reported the outcomes of eight patients diagnosed with stage 4b retinoblastoma between 2000 and 2006 treated with autologous HCT.^[17] Seven of the patients had leptomeningeal disease and one had only direct extension to the CNS via the optic nerve. At

the time of diagnosis of intra-ocular retinoblastoma, three patients already had stage 4b disease; the other five patients developed metastatic disease at a median of 12 months (range 3-69 months). Two patients progressed prior to HCT and one patient died of toxicity during induction chemotherapy. Of the five patients that underwent HCT, two were event-free at 40 and 101 months. One of the event-free survivors received radiation therapy (external beam plus intrathecal radioimmunotherapy) and the other did not receive any form of radiation. Three patients had tumor recurrence at 3, 7, and 10 months post-HCT. The authors concluded that HCT may be beneficial for some patients with stage 4b retinoblastoma, but that longer follow-up is necessary to determine whether it is curative in this population.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

In 2020, the American Society for Transplantation and Cellular Therapy (ASTCT), previously the American Society for Blood and Marrow Transplantation (ASBMT), published consensus guidelines for clinically appropriate indications for hematopoietic cell transplantation (HCT) based on best prevailing evidence. The following was excerpted from original publication. Indications for HCT in pediatric patients with the solid tumors types addressed in this review are outlined in Table 1.

Table 1. ASTCT 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

ASTCT: American Society for Transplantation and Cellular Therapy; 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

For Ewing sarcoma, the National Comprehensive Cancer Network (NCCN) guidelines for bone cancer (v.1.2026) state the following:^[66]

“High-dose therapy followed by hematopoietic stem cell transplant (HDT/HCT) has been evaluated in patients with localized as well as metastatic disease. HDT/HCT has been associated with potential survival benefit in patients with non-metastatic disease. However, studies that have evaluated HDT/HCT in patients with primary metastatic disease have shown conflicting results.... HDT/HCT 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.”

SUMMARY

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Single Autologous Hematopoietic Cell Transplantation

It appears that the use of autologous hematopoietic cell transplantation may improve overall health outcomes when used to for initial treatment of high-risk Ewing’s sarcoma, to consolidate remissions or treat residual, recurrent or refractory Ewing’s sarcoma. Therefore, allogeneic HCT may be considered medically necessary in this population.

There is enough research to show improved event-free survival (EFS) and overall survival (OS) with use of single autologous hematopoietic cell transplantation (HCT) for treatment of children with neuroblastoma as first-line treatment, or as treatment of recurrent or refractory neuroblastoma. Therefore, use of single autologous HCT may be considered medically necessary in this population.

There is enough research to show that there is a potential benefit of hematopoietic cell transplantation (HCT) in some high-risk, relapsed Wilms tumor patients; therefore use of autologous HCT in this population may be considered medically necessary.

It appears that autologous hematopoietic cell transplantation (HCT) may improve overall health outcomes for some people with metastatic retinoblastoma. Therefore use of autologous HCT in this population may be considered medically necessary.

There is not enough research to show that autologous hematopoietic cell transplantation (HCT) is beneficial in the initial treatment of low- or intermediate risk Ewing’s sarcoma family of tumors (ESFT), initial treatment of low- or intermediate-risk neuroblastoma, or other solid tumors of childhood, including but not limited to osteosarcoma, retinoblastoma without metastasis, rhabdomyosarcoma, and Wilms tumor, other than recurrent, high-risk. Therefore, use of autologous HCT in this population is considered investigational.

Tandem Autologous Hematopoietic Cell Transplantation

Few studies directly comparing single autologous to tandem autologous hematopoietic cell transplantation (HCT) for high-risk neuroblastoma have been published; however, the evidence suggests that the use of tandem autologous for high-risk neuroblastoma may result in event-free survival (EFS) rates superior to those reported with the use of single autologous HCT. Therefore, for pediatric patients with high-risk neuroblastoma who meet the criteria, treatment with tandem HCT may be considered medically necessary.

There is not enough research to show that tandem autologous hematopoietic cell transplantation (HCT) is beneficial in the treatment of pediatric solid tumors other than high-

risk neuroblastoma. Therefore, with the exception of high-risk neuroblastoma, use of tandem autologous HCT is considered investigational for the treatment of pediatric solid tumors.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

There is not enough research to show that allogeneic hematopoietic cell transplantation (HCT) is beneficial in the treatment of pediatric solid tumors, including tumors that relapse after autologous transplant or fail to respond. Therefore, use of allogeneic HCT in the treatment of pediatric solid tumors is considered investigational.

REFERENCES

1. Hale GA. Autologous hematopoietic stem cell transplantation for pediatric solid tumors. *Expert Rev Anticancer Ther*. 2005;5(5):835-46. PMID: 16221053
2. Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. *Oncologist*. 2003;8(3):278-92. PMID: 12773750
3. Physician Data Query (PDQ®). Neuroblastoma treatment: health professional version. National Cancer Institute. 04/28/2025 [cited 09/18/2025]. 'Available from:' <http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/healthprofessional>.
4. Shimada H, Ambros IM, Dehner LP, et al. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. *Cancer*. 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*. 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*. 2005;353(21):2243-53. PMID: 16306521
7. Barker LM, Pendergrass TW, Sanders JE, et al. Survival after recurrence of Ewing's sarcoma family of tumors. *J Clin Oncol*. 2005;23(19):4354-62. PMID: 15781881
8. Physician Data Query (PDQ®). Childhood rhabdomyosarcoma treatment: health professional version. National Cancer Institute. 04/11/2025 [cited 09/18/2025]. 'Available from:' <http://www.cancer.gov/cancertopics/pdq/treatment/childrhabdomyosarcoma/healthprofessional>.
9. Admiraal R, Van der Paardt M, Kobes J. High dose chemotherapy for children with stage IV rhabdomyosarcoma (protocol). *Cochrane Database of Systematic Reviews*. 2007(Issue 3). PMID:
10. 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*. 1997;19(3):227-31. PMID: 9028550
11. 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*. 2004;22(14):2885-90. PMID: 15254057
12. Dallorso S, Dini G, Faraci M, et al. SCT for Wilms' tumour. *Bone Marrow Transplant*. 2008;41 Suppl 2:S128-30. PMID: 18545233
13. 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*. 2008;51(1):23-8. PMID: 18293386
14. Fagioli F, Biasin E, Mereuta OM, et al. Poor prognosis osteosarcoma: new therapeutic approach. *Bone Marrow Transplant*. 2008;41 Suppl 2:S131-4. PMID: 18545234
15. Physician Data Query (PDQ®). Osteosarcoma/Malignant fibrous histiocytoma of bone treatment: health professional version. National Cancer Institute; last updated June 8, 2022. 12/02/2024 [cited 09/18/2025]. 'Available from:'
<http://www.cancer.gov/cancertopics/pdq/treatment/osteosarcoma/healthprofessional>.
16. Physician Data Query (PDQ®). Retinoblastoma treatment: health professional version. National Cancer Institute; last updated August 9, 2022. 04/03/2025 [cited 09/18/2025]. 'Available from:'
<http://www.cancer.gov/cancertopics/pdq/treatment/retinoblastoma/healthprofessional>.
17. Dunkel IJ, Chan HS, Jubran R, et al. High-dose chemotherapy with autologous hematopoietic stem cell rescue for stage 4B retinoblastoma. *Pediatr Blood Cancer*. 2010;55(1):149-52. PMID: 20486181
18. Abramson DH, Shields CL, Munier FL, et al. Treatment of Retinoblastoma in 2015: Agreement and Disagreement. *JAMA ophthalmology*. 2015;133(11):1341-7. PMID: 26378747
19. Żebrowska U, Balwierz W, Wechowski J, et al. Survival Benefit of Myeloablative Therapy with Autologous Stem Cell Transplantation in High-Risk Neuroblastoma: A Systematic Literature Review. *Target Oncol*. 2024;19(2):143-59. PMID: 38401028
20. 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*. 1999;341(16):1165-73. PMID: 10519894
21. 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*. 2009;27(7):1007-13. PMID: 19171716
22. 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*. 2005;6(9):649-58. PMID: 16129365
23. 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*. 2005;44(4):348-57. PMID: 15546135
24. Yalcin B, Kremer LC, Caron HN, et al. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. *The Cochrane database of systematic reviews*. 2013;8:CD006301. PMID: 23970444
25. Ratko TA, Belinson SE, Brown HM et al. Hematopoietic stem-cell transplantation in the pediatric population. Comparative Effectiveness Review No 48. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10058.) AHRQ Publication No. 12-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality. February 2012. <https://effectivehealthcare.ahrq.gov/products/stem-cell-children/research-protocol>. PMID:
26. Park JR, Kreissman SG, London WB, et al. Effect of Tandem Autologous Stem Cell Transplant vs Single Transplant on Event-Free Survival in Patients With High-Risk

Neuroblastoma: A Randomized Clinical Trial. *JAMA*. 2019;322(8):746-55. PMID: 31454045

27. 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*. 2010;25(5):691-7. PMID: 20436703
28. 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*. 2008;41 Suppl 2:S118-27. PMID: 18545256
29. 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*. 2007;22 Suppl:S66-72. PMID: 17923758
30. 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*. 2006;24(18):2891-6. PMID: 16782928
31. 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. *Journal of pediatric surgery*. 2005;40(6):936-41; discussion 41. PMID: 15991174
32. 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. *Journal of pediatric hematology/oncology*. 2003;25(12):934-40. PMID: 14663275
33. 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*. 2002;20(9):2284-92. PMID: 11980999
34. Grupp SA, Stern JW, Bunin N, et al. Rapid-sequence tandem transplant for children with high-risk neuroblastoma. *Medical and pediatric oncology*. 2000;35(6):696-700. PMID: 11107149
35. Prete A, Lanino E, Saglio F, et al. Phase II Study of Allogeneic Hematopoietic Stem Cell Transplantation for Children with High-Risk Neuroblastoma Using a Reduced-Intensity Conditioning Regimen: Results from the AIEOP Trial. *Transplant Cell Ther*. 2024;30(5):530.e1-30.e8. PMID: 38460729
36. Sung KW, Park JE, Chueh HW, et al. Reduced-intensity allogeneic stem cell transplantation for children with neuroblastoma who failed tandem autologous stem cell transplantation. *Pediatr Blood Cancer*. 2011;57(4):660-5. PMID: 21681924
37. Meyers PA. High-dose therapy with autologous stem cell rescue for pediatric sarcomas. *Curr Opin Oncol*. 2004;16(2):120-5. PMID: 15075902
38. Ramamurthy A, Connolly EA, Mar J, et al. High-dose chemotherapy for Ewing sarcoma and Rhabdomyosarcoma: A systematic review by the Australia and New Zealand sarcoma association clinical practice guidelines working party. *Cancer Treat Rev*. 2024;124:102694. PMID: 38325070
39. Koch R, Gelderblom H, Haveman L, et al. High-Dose Treosulfan and Melphalan as Consolidation Therapy Versus Standard Therapy for High-Risk (Metastatic) Ewing Sarcoma. *J Clin Oncol*. 2022;40(21):2307-20. PMID: 35427190
40. Dirksen U, Brennan B, Le Deley MC, et al. High-Dose Chemotherapy Compared With Standard Chemotherapy and Lung Radiation in Ewing Sarcoma With Pulmonary Metastases: Results of the European Ewing Tumour Working Initiative of National Groups, 99 Trial and EWING 2008. *J Clin Oncol*. 2019;37(34):3192-202. PMID: 31553693

41. 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*. 2001;19(11):2812-20. PMID: 11387352
42. Gardner SL, Carreras J, Boudreau C, et al. Myeloablative therapy with autologous stem cell rescue for patients with Ewing sarcoma. *Bone Marrow Transplant*. 2008;41(10):867-72. PMID: 18246113
43. Ladenstein R, Potschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol*. 2010;28(20):3284-91. PMID: 20547982
44. Admiraal R, van der Paardt M, Kobes J, et al. High-dose chemotherapy for children and young adults with stage IV rhabdomyosarcoma. *The Cochrane database of systematic reviews*. 2010(12):CD006669. PMID: 21154373
45. 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. *Journal of pediatric hematology/oncology*. 2001;23(5):272-6. PMID: 11464981
46. Carli M, Colombatti R, Oberlin O, et al. High-dose melphalan with autologous stem-cell rescue in metastatic rhabdomyosarcoma. *J Clin Oncol*. 1999;17(9):2796-803. PMID: 10561355
47. 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*. 2008;50(4):739-45. PMID: 18286501
48. 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*. 2010;46(9):1588-95. PMID: 20338746
49. Kremens B, Gruhn B, Klingebiel T, et al. High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. *Bone Marrow Transplant*. 2002;30(12):893-8. PMID: 12476282
50. Presson A, Moore TB, Kempert P. Efficacy of high-dose chemotherapy and autologous stem cell transplant for recurrent Wilms' tumor: a meta-analysis. *Journal of pediatric hematology/oncology*. 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. *Medical and pediatric oncology*. 1994;22(1):11-4. PMID: 8232074
52. 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*. 1998;16(10):3295-301. PMID: 9779704
53. Kullendorff CM, Bekassy AN. Salvage treatment of relapsing Wilms' tumour by autologous bone marrow transplantation. *Eur J Pediatr Surg*. 1997;7(3):177-9. PMID: 9241510
54. Delafoy M, Verschuur A, Scheleirmacher G, et al. High-dose chemotherapy followed by autologous stem cell rescue in Wilms tumors: French report on toxicity and efficacy. *Pediatr Blood Cancer*. 2022;69(3):e29431. PMID: 34811873
55. 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*. 2017;52:1549-55. PMID: 28869618
56. 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*. 2002;20(8):2150-6. PMID: 11956277
 57. 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*. 2020;37(4):337-43. PMID: 32151185
 58. Kang SH, Kim W, Lee JS, et al. High-dose chemotherapy followed by autologous stem cell transplantation in pediatric patients with relapsed osteosarcoma. *Pediatr Blood Cancer*. 2023;70(4):e30233. PMID: 36751119
 59. Dunkel IJ, Aledo A, Kernan NA, et al. Successful treatment of metastatic retinoblastoma. *Cancer*. 2000;89(10):2117-21. PMID: 11066053
 60. Jubran RF, Erdreich-Epstein A, Butturini A, et al. Approaches to treatment for extraocular retinoblastoma: Children's Hospital Los Angeles experience. *Journal of pediatric hematology/oncology*. 2004;26(1):31-4. PMID: 14707710
 61. Kremens B, Wieland R, Reinhard H, et al. High-dose chemotherapy with autologous stem cell rescue in children with retinoblastoma. *Bone Marrow Transplant*. 2003;31(4):281-4. PMID: 12621463
 62. 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*. 2005;35(8):763-6. PMID: 15750608
 63. Namouni F, Doz F, Tanguy ML, et al. High-dose chemotherapy with carboplatin, etoposide and cyclophosphamide followed by a haematopoietic stem cell rescue in patients with high-risk retinoblastoma: a SFOP and SFGM study. *Eur J Cancer*. 1997;33(14):2368-75. PMID: 9616283
 64. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of metastatic retinoblastoma. *Ophthalmology*. 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*. 2010;55(1):55-9. PMID: 20486171
 66. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Bone Cancer. Version 1.2026. [cited 09/18/2025]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf.

CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion

	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: May 2010