

Molina Clinical Policy

Hematopoietic Stem Cell Transplantation for Solid Tumors:

Policy No. 457

Last Approval: 02/12/2025
Next Review Due By: June 2025



DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy covers hematopoietic stem cell transplantation for the following diseases:

Ewing's Sarcoma	Neuroblastomas
Germ Cell Tumors	Wilms Tumor

Hematopoietic Stem Cell Transplantation (HSCT) refers to transplantation of hematopoietic stem cells from a donor into a patient. Hematopoietic stem cells are immature cells that can develop into any of the three types of blood cells (red cells, white cells, or platelets). Hematopoietic stem cells are created in the bone marrow and are found there, in peripheral blood, and in high concentrations in umbilical-cord blood. HSCT can be autologous (using the patient's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. As HLA variability increases, transplant-related morbidity and mortality (including graft rejection and graft-versus-host disease) also increases. HSCT can be utilized in the treatment of a variety of diseases from blood cancers to solid tumors (³NMDP date unknown).

Ewing's Sarcoma (ES) is a small round cell tumor that originates in bone or soft tissue. ES is a part of the Ewing's Sarcoma Family of Tumors (ESFT) which includes Ewing tumor of bone, extraosseous Ewing, primitive neuroectodermal tumors, and Askin tumors, as all these malignancies derive from the same type of stem cell. ES is the second most common bone tumor in children and adolescents with a median age of 15 years old but can occur at any age. The most common osseous sites of ES are the lower extremities and pelvis, with the most common extraosseous sites being extremities and trunk. Approximately 25% of patients will have metastatic disease at diagnosis. According to the National Cancer Institute (2024) ES can be classified into low risk (localized tumor with no spread beyond the primary site or regional lymph node involvement), intermediate risk (tumor has spread to lungs), and high risk (tumor has spread beyond to bone, bone marrow and/or other tissue). Standard treatment of ESFT includes systemic chemotherapy in conjunction with either surgery or radiation, or both for local tumor control. The prognosis for patients with high-risk tumors treated with conventional chemotherapy, radiation and surgery remains poor, with long-term survival rates for patients with metastatic disease less than 35%. Dose-intensive chemotherapy regimens and HSCT have been investigated in patients with high-risk ESFT to improve survival (Gebhardt et al. 2024).

Germ Cell Tumors (GCT) are tumors that arise from the germ cells, the embryonic cells that develop into reproductive organs. GCTs may be benign or malignant and can form in the reproductive organs or extragonadally. Most germ cell tumors occur in the testicles or the ovaries; however, in rare cases, they can occur in other areas of the body such as chest, abdomen, and brain. GCTs are classified according to their site, histology, stage, prognosis, and response to chemotherapy. Germ cell tumors include germinomas, teratomas, embryonal carcinoma, yolk sac (endodermal sinus) tumors, and choriocarcinomas. GCTs can manifest in varied sites and the treatment for each type is different. Treatment generally involves a combination of surgery, chemotherapy, and radiation. Autologous HSCT has shown to have a powerful role in the treatment of male GCTs. Patients who fail first-line treatment usually receive salvage chemotherapy. This method of high dose chemotherapy and autologous HSCT are an effective treatment in this

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context (Losco et al. 2024). Ovarian germ cell tumors, which are rare, include dysgerminomas and nondysgerminomas, which include immature teratomas, embryonal cell carcinoma, yolk sac tumors, primary ovarian (nongestational) choriocarcinomas, polyembryoma, and mixed germ cell tumors. Due to the rarity of these tumors, the treatment often follows the recommendations for testicular germ cell tumors, particularly in reference to the treatment of refractory or relapsed ovarian germ cell tumors (Gershenson 2025).

Neuroblastomas are tumors primarily found in children 5 years and younger, that arise from primitive sympathetic ganglion cells and vary in location, histology, and biological characteristics. Since neuroblastomas can arise anywhere in the sympathetic nervous system, locations are numerous with the adrenal gland and abdomen being the most common sites. Neuroblastomas are staged according to the International Neuroblastoma Risk Group Staging System (Montclair et al. 2009) defined as L1 (localized tumor not involving vital structures as defined by the list of IDRFs and confined to one body compartment), L2 (locoregional tumor with presence of one or more IDRFs), M (distant metastatic disease), MS (metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow). HSCT is a treatment modality typically used in combination with aggressive chemotherapy and radiation in patients diagnosed with high-risk neuroblastoma (¹⁻²Shohet et al. 2024).

Wilms Tumor is a type of kidney cancer and is the most common renal malignancy in children, with the average age at diagnosis between 3-5 years, and accounts for nearly 650 new cases in the United States annually (Leslie et al. 2023). Wilms Tumor can occur unilaterally in one kidney or bilaterally in both kidneys and can metastasize to other locations in the body. While the proliferation of the cells that form Wilms Tumor begins gestationally, the cells do not mature until around age 3 and often do not produce noticeable symptoms in young children. Often the first sign noticed by parents is an abdominal mass when assisting the child with activities of daily living. Older children sometimes exhibit more noticeable symptoms such as pain, anemia, fever, blood in the urine, nausea, vomiting, constipation, loss of appetite, shortness of breath, and high blood pressure (NORD 2023). Management of Wilms tumor is determined by tumor histology, disease stage, and patient age. For many who are newly diagnosed, management includes nephrectomy and chemotherapy with or without radiation therapy. Radiation is reserved for patients with an increased risk of recurrence, advanced stage disease, anaplastic histology, metastases, or relapse. Following treatment, screening for recurrence includes abdominal ultrasound every 3 months for 3 to 6 years. Wilms Tumor may be assigned Stage I – V based on tumor characteristics and location (Leslie et al. 2023).

COVERAGE POLICY

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be reviewed by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, State regulations, and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.

Please see MCP-459 Pre-Transplant and Transplant Evaluation for pre-transplant criteria and transplant evaluation criteria that must be met prior to hematopoietic stem cell transplantation (HSCT).

I. Ewing's Sarcoma

Medically Necessary

1. *Autologous HSCT* may be **considered medically necessary** when **ALL** MCP 459 Transplant Evaluation criteria are met AND treatment is intended for ONE of the following:
 - a. Initial treatment of high-risk Ewing's sarcoma (defined as metastatic disease, unfavorable tumor location [e.g., primary tumor site in the axial skeleton, including pelvis], larger tumor size, or older age of the Member)

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- b. Salvage therapy for recurrent or refractory Ewing's sarcoma (defined as a tumor that does not achieve a complete remission after initial standard-dose chemotherapy).

2. *Repeat Autologous HSCT* may be considered medically necessary in cases of primary graft failure indicated by no signs of engraftment by 42 days after the transplant OR failure to engraft*

*NOTE: Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds $0.5 \times 10^9/L$ or $ANC > 500/uL$ at any time after transplantation. (*NMDP date unknown).

Investigational, Unproven, and/or Not Medically Necessary

1. A second or repeat Autologous HSCT due to persistent, progressive, or relapsed disease
2. Allogenic HSCT
3. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation.

II. Germ Cell Tumors

Medically Necessary

1. *Single Autologous HSCT* may be **considered medically necessary** as a treatment of primary malignant germ cell tumors in individuals treated with chemotherapy when ALL MCP 459 Transplant Evaluation criteria are met AND treatment is intended for ONE of the following:
 - a. A partial or poor initial response
 - b. Short remission
 - c. Refractory germ cell tumors
 - d. Persistent or Relapsed disease
2. *Tandem or Sequential Autologous HSCT* in conjunction with high-dose chemotherapy may be **considered medically necessary** for the treatment of primary malignant germ cell tumors in individuals in which standard chemotherapy treatment was ineffective, when ALL MCP 459 Transplant Evaluation criteria are met AND treatment is intended for ONE of the following:
 - a. A partial response
 - b. Refractory germ cell tumors
 - c. Persistent or Relapsed disease
3. *Repeat Autologous HSCT* may be **considered medically necessary** due to primary graft failure OR failure to engraft*

*NOTE: Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds $0.5 \times 10^9/L$ or $ANC > 500/uL$ at any time after transplantation. (*NMDP date unknown)

Investigational, Unproven, and/or Not Medically Necessary

1. Single Autologous HSCT as first-line treatment of poor prognosis germ-cell tumors
2. Allogenic HSCT to treat germ-cell tumors as therapy after a previously failed autologous hematopoietic stem-cell transplantation

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3. Repeat or second Autologous HSCT due to persistent, progressive, or relapsed disease
4. Tandem or Sequential Autologous HSCT to treat any germ cell tumors of any stage other than primary testicular cancer
5. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation.

III. Neuroblastoma

Medically Necessary

1. *Single Autologous HSCT* may be **considered medically necessary** for the initial treatment of neuroblastoma when ALL MCP 459 Transplant Evaluation criteria are met and ANY of the following are present:
 - a. International Neuroblastoma Staging System (INSS) Stage 2 or 3 at diagnosis and MYCN amplification (>4x above reference)
 - b. INSS Stage 4 at diagnosis with MYCN amplification (>4x above reference) with ANY of the following: age >18 months at diagnosis, age 12-18 months with unfavorable characteristics, OR metastatic disease at diagnosis
2. *Single Autologous HSCT* may be **considered medically necessary** for the treatment of neuroblastoma when ALL MCP 459 Transplant Evaluation criteria are met AND treatment is intended for ONE of the following:
 - a. Persistent or relapsed neuroblastoma
 - b. Primary refractory neuroblastoma
3. *Tandem or Sequential Autologous HSCT* may be **considered medically necessary** for the treatment of high-risk neuroblastoma
4. *Repeat Autologous HSCT* may be **considered medically necessary** in the case of primary graft failure OR failure to engraft*

*NOTE: Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds 0.5 x 10⁹/L or ANC > 500/uL at any time after transplantation. (¹NMDP date unknown)

Investigational, Unproven, and/or Not Medically Necessary

1. Single Autologous HSCT as the initial treatment of low or intermediate risk neuroblastoma
2. Single or Tandem Allogeneic HSCT for the treatment of neuroblastoma
3. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation.

IV. Wilms Tumor

Medically Necessary

1. *Single Autologous HSCT* may be **considered medically necessary** for the treatment of Wilms Tumor when ALL MCP 459 Transplant Evaluation criteria are met and ANY of the following criteria are present:

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- a. Recurrent or refractory disease after initial treatment with four or more chemotherapeutic agents
 - b. Multiple relapses or progression on salvage therapy
2. *Repeat Autologous HSCT* may be **considered medically necessary** in the case of primary graft failure OR failure to engraft*

*Note: Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds $0.5 \times 10^9/L$ or $> ANC500$ at any time after transplantation.

Investigational, Unproven, and/or Not Medically Necessary

1. Allogeneic HSCT
2. Tandem Autologous HSCT
3. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Ewing's Sarcoma

Ratko et al. (2012) conducted a comparative effectiveness review on the use of hematopoietic stem cell transplant (HSCT) in the pediatric population. The report was published by the Blue Cross and Blue Shield Association Technology Evaluation Center for the Agency for Healthcare Research and Quality (AHRQ). Conclusions for Ewing Sarcoma Family of Tumors (ESFT) indicated the following: Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk ESFT. The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.

Ferrari et al. (2011) conducted a large study and reported results of the Italian Sarcoma Group/Scandinavian Sarcoma Group III protocol, a multicenter, multi-country clinical trial involving 300 participants with ESFT. At a median follow-up of 64 months, five-year overall survival (OS) and event-free survival (EFS) were 75% and 69%, respectively. Five-year EFS for those treated with high-dose chemotherapy were 75% for good responders and 72% for partial responders, and 33% for partial responders who did not receive high-dose chemotherapy.

Ladenstein et al. (2010) conducted a large study named the EURO-EWING-Intergroup-EE99 R3 trial enrolled 281 patients with primary disseminated metastatic Ewing sarcoma. Patients were treated with six cycles of vincristine, ifosfamide, doxorubicin, and etoposide followed by high-dose therapy and autologous stem cell transplant and after a median follow-up of 3.8 years, EFS and OS at 3 years for all 281 patients were 27% +/- 3% and 34% +/- 4% respectively. Factors such as the presence and number of bone lesions, primary tumor volume greater than 200 mL, and age older than 14 years, additional pulmonary metastases, and bone marrow involvement were identified as independent prognostic factors.

Germ Cell Tumors

Losco et al. (2024) conducted a multicenter retrospective analysis of patients ≥ 15 years old with relapsed/refractory GCTs who received HSCT between the years 2010 to 2022. A total of 114 patients were included in the analysis with 66% of patients with non-seminoma histology (66%), and varied sites included the testis (65%), retroperitoneum (17%), and mediastinum (9%). Prior to receiving HSCT 82% received ≥ 2 lines of chemotherapy, and 45% received 2

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consecutive courses of HSCT. The median engraftment time was 12 days (d) (r8;25) for neutrophils and 15 d (r6;58) for platelets. One hundred patients were evaluable for survival, resulting in 12- and 24-months 67% and 64% OS, and 56% and 54% PFS, respectively. Platinum-refractory disease patients had worse OS and PFS. Of the original 114 patients, 18 remained alive and without relapsing beyond 5 years of follow-up. The authors concluded that the analysis revealed some patients with refractory/relapsed metastatic GCT are curable by HSCT, which is a safe and effective treatment.

Kilari et al. (2019) conducted a retrospective analysis of the survival trends as reported through the Center for International Blood and Marrow Transplant Research. A total of 2395 patients with male GCTs received autologous HSCT between 1990 and 2015. Trends and outcomes were analyzed by year of transplantation for intervals 1990 to 1994 (N = 288), 1995 to 1999 (N = 351), 2000 to 2004 (N = 376), 2005 to 2009 (N = 509), and 2010 to 2015 (N = 871). Multivariate analysis was restricted to the subset from 2000 to 2015 with research-level data (n = 267). The authors highlighted that while the curative potential of autologous HSCT in male GCTs is established, the optimal timing and number (single transplant versus tandem transplants versus triple transplants) of autologous HSCT are controversial, with wide practice variations. Six-hundred and thirty-three patients (26%) had primary extragonadal GCT, and 1167 (49%) underwent tandem transplants. The 3-year progression-free (PFS) and overall survival (OS) improved from 24% (95% confidence interval [CI], 18% to 31%) and 35% (95% CI, 29% to 40%), respectively, in 1990 to 1994 to 47% (95% CI, 43% to 50%) and 54% (95% CI, 50% to 57%), respectively, in 2010 to 2015 (P < .0001). Tandem transplant recipients were more likely than single transplant recipients to undergo autologous HSCT as first salvage treatment, and the proportion of tandem transplants increased from 38% of all autologous HSCTs in 2000 to 2004 to 77% in 2010 to 2015. The authors found the following factors associated with inferior PFS and OS: nonseminoma histology, residual disease at autologous HSCT, >1 line of pretransplantation chemotherapy, and single transplant versus tandem transplant. Overall, the authors concluded that post-transplantation survival has improved over the last three decades due to increased use of tandem transplants and use of autologous HSCT earlier in the disease course.

De Giorgi et al. (2017) conducted a retrospective analysis of female patients with GCTs that were treated with salvage high dose chemotherapy (HDT). The salvage high dose chemotherapy was often accompanied by HSCT. The analysis reviewed 60 patients registered with the European Society for Blood and Marrow Transplantation between the years of 1985 – 2013. The patients were age \geq 15 years with a diagnosis of female GCT. Patients with extragonadal GCT, dysgerminomas and non-dysgerminomas (i.e., embryonal carcinoma, choriocarcinoma, yolk sac tumor, immature teratoma, and mixed GCT) were included in the review. In total, 11 (18%) patients were treated with 15 courses of a HDT regimen, 23 (38%) patients received 30 courses, and 26 (43%) patients 45 courses. A total of 61 courses of HDT in 37 patients were supported by HSCT reinfusion, with one course supported by both bone marrow and HSCT reinfusion. The results revealed that out of 51 evaluable cases, 17 (33%) patients achieved a complete response (CR), 8 (16%) a marker-negative partial remission (PRm-), 5 (10%) a marker-positive partial remission, 5 (10%) stable disease, and 13 (25%) progressive disease. In total, 25 of 60 patients (42%) were progression-free following HDT at a median follow-up of 87 months (range 3–219 months). While the limitations of this study were its retrospective nature, small case cohort, and a large time period of review, the results supported HDT, particularly as initial salvage, can achieve long-term disease-free survival and cure potential in patients with recurrent female GCT.

Lorch et al. (2011;2012) compared single- versus sequential high dose chemotherapy with autologous HSCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors. This represented the first salvage therapy received in 86% of the patients in arm A and 85% in arm B, whereas 14% (arm A) and 15% (arm B) had received one or more previous salvage regimens prior to randomization. With a median follow-up time of 36 months, 109 (52%) of 211 patients were alive, and 91 (43%) of 211 patients were progression free. At 1 year, event-free, progression-free, and overall survival rates were 40%, 53%, and 80%, respectively, in arm A compared with 37%, 49%, and 61%, respectively, in arm B (p >0.05 for all comparisons). Long-term results were reported in 2012 from this study indicated five-year PFS as 47% (95% CI, 37%-56%) in arm A and 45% (95% CI, 35%-55%) in arm B (hazard ratio, 1.16; 95% CI, 0.79-1.70; p=.454). Five-year OS was 49% (95% CI, 40%-59%) in arm A and 39% (95% CI, 30%-49%) in arm B (hazard ratio, 1.42; 95% CI, 0.99-2.05; p=.057). Results showed that patients with relapsed or refractory germ-cell tumors can achieve durable long-term survival after single as well as sequential HSCT and that fewer early deaths related to toxicity translated into superior long-term OS after sequential HSCT.

Neuroblastoma

Zebrowska et al. (2024) conducted a meta – analysis and systematic literature review assessing the survival benefit of myeloablative therapies (MAT) with autologous HSCT in high – risk neuroblastoma. A total of 41 publications fit

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inclusion criteria of comparative studies of patients with high-risk neuroblastoma, regardless of design, where MAT+HSCT was compared with treatment that did not include MAT+HSCT. Inclusion criteria also stipulated that at least one comparative survival outcome [EFS, progression-free survival (PFS), relapse-free survival (RFS) and/or OS] should have been reported in the study. Seven publications reported on 4 RCTs and 34 publications reported on 30 non-randomized studies. The meta-analysis of the RCTs showed a statistically significant difference in EFS in favor of MAT+HSCT over conventional chemotherapy or no further treatment (HR = 0.78, 95% CI 0.67–0.91, $p = 0.001$) and a non-significant trend favoring MAT+ASCT for OS (HR = 0.86, 95% CI 0.73–1.00, $p = 0.05$). The non-RCT comparative studies supported the evidence from the RCTs; however, not all non-RCT studies reported survival benefit for MAT+ASCT. Despite there being limited comparative evidence for the survival benefit of MAT+HSCT followed by anti-GD2 immunotherapy versus anti-GD2 therapy alone without prior MAT+HSCT, evidence suggests that in patients treated with anti-GD2 immunotherapy, prior tandem HSCT improves both EFS and OS. The main limitation of the analysis is the heterogeneity of the therapies used, especially as, different induction schedules may influence the response to MAT+HSCT, additionally baseline characteristics were often not reported in detail nor was response to treatment reported consistently. The authors concluded that evidence supports the use of MAT+HSCT for reducing the risk of relapse in patients with high-risk neuroblastoma, and that while the OS benefit trend lacks significance, limited evidence suggests poorer outcomes when MAT+HSCT is omitted prior to anti-GD2 immunotherapy. The summation of the results suggest MAT+HSCT should remain an integral part of multimodal therapy until further evidence emerges.

Park et al. (2019) completed a RCT to determine if patients with high-risk neuroblastoma had improved EFS with tandem autologous HSCT compared to single autologous HSCT. The RCT included a total of 652 eligible patients with a median age of 37.2 months; however, only 355 patients were randomized due to being excluded from randomization for either physician/parent preference ($n=207$), being ineligible for randomization ($n=62$), being nonrandomly assigned ($n=27$), or not undergoing therapy ($n=1$). Of the 355 patients that were randomized, 176 were randomized to the tandem transplant group and 179 were randomized to the single transplant group. Patients were randomized on a 1:1 basis before receiving consolidation therapy. Those with more favorable prognoses were assigned to receive a single transplant and their data was not included in the analyses. To receive a tandem transplant, patients had to have “no clinical evidence of neuroblastoma progression, available peripheral blood stem cell product, resolution of acute toxicity from the first transplant, adequate cardiac, kidney, hematopoietic, and hepatic function, no uncontrolled infection, and no history of moderate or severe sinusoidal obstruction syndrome during the first transplant.” All patients received radiotherapy following transplant recovery at the primary, residual, and/or metaiodobenzylguanidine-positive metastatic sites. The primary outcome of the RCT was to observe EFS from the time of randomization to relapse, progression, secondary malignancy, or death from any cause. Overall, 3-year EFS for all eligible patients ($n=652$) was 51.1% and 3-year EFS for the randomized patients ($n=355$) was 54.9%. The 3-year EFS for patients randomized to the tandem transplant group was 61.6% compared to 48.4% for those randomized to the single transplant group. EFS from time of randomization to the first event was noted to be higher in the tandem transplant group. The 3-year OS for all randomized patients was 71.6%. The 3-year OS for patients in the tandem transplant group was 74.1% compared to 69.1% for the single transplant group. After consolidation therapy, 250 of the randomized patients ($n=121$ tandem transplant; $n=129$ single transplant) received immunotherapy in the form of isotretinoin plus anti-GD2 chimeric antibody and cytokines. The 3-year EFS and OS following immunotherapy was higher in the tandem transplant group (EFS=73.3%; OS=84.0%) compared to the single transplant group (EFS=54.7%; OS=73.5%). In terms of treatment-related morbidity and mortality, tandem transplants were associated with less complications, such as infection, organ injury, and death compared to single transplants. Researchers noted that limitations of this study included a lack of randomization for a large proportion of included patients, tandem transplants are associated with longer hospital stays, newer therapies are available for relapsed neuroblastoma that have the potential to improve survival, and “the higher EFS rate associated with tandem transplant is relevant only within the context of the total therapy delivered.” Researchers note that approximately 10% of patients in the study did not progress beyond the induction phase due to disease progression or death.

Berthold et al. (2018) completed an open-label, randomized trial to determine the long-term outcomes of patients with high-risk neuroblastoma following high-dose chemotherapy (HDT) with autologous HSCT or maintenance therapy for consolidation. Patients were eligible for inclusion if they had a “1) newly diagnosed neuroblastoma according to the INSS, 2) high-risk defined as stage 4 disease in patients aged ≥ 1 to < 21 years or MYCN-amplified tumors of patients with stage 1, 2, 3, or 4S disease aged 6 months to < 21 years or stage 4 disease and age < 1 year with MYCN amplification, and 3) written informed consent from the parents or legal guardian.” Exclusion criteria included additional concomitant non-protocol anti-cancer therapies. A total of 295 patients were randomized prior to the end of induction

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chemotherapy. Patients were assigned to either the intention-to-treat (ITT), as-treated-group (AT), or treated-as-randomized (TAR) groups as there were minor deviations from the treatment protocol allowed. The ITT group consisted of all 295 randomized patients with 149 in the autologous HSCT group and 146 in the maintenance therapy group. The AT group consisted of 212 patients (n=110 autologous HSCT; n=102 maintenance therapy) assigned to the group of their treatment, regardless of how they were initially randomized. The TAR group consisted of 145 patients (n=75 autologous HSCT; n=70 maintenance therapy) based on their original randomization. The primary outcome observed was EFS and the secondary outcome observed was OS. Median follow-up was 13.1 years for ITT and TAR and 13.0 years for AT. The 10-year EFS was 34±3% for ITT, 38±3% for AT, and 38±4% for TAR. The 10-year OS was 40±3% for ITT, 41±3% for AT, and 42±4% for TAR. Multivariate analysis showed autologous HSCT had better EFS in the ITT subgroups in patients who had complete or very good partial response before randomization, raised lactate dehydrogenase (LDH) at diagnosis, MYCN amplification, stage 4 and age > 1 year, and ch14.18 treatment as further consolidation. EFS and OS was superior in the AT subgroup for autologous HSCT subgroups with complete or very good partial response before randomization, raised LDH at diagnosis, and MYCN amplification. EFS and OS were significantly better for autologous HSCT in the TAR subgroup in those with complete or very good partial response before randomization, raised LDH at diagnosis, normal MYCN, amplified MYCN, and stage 4 disease and age > 1 year. Antibody ch14.18 treatment showed significant differences in EFS and trends for improved OS, particularly in those receiving autologous HSCT. A higher number of recurrences, defined as relapse or disease progression, was noted in the maintenance therapy group when compared to the autologous HSCT group; however, liver recurrences were more common in the autologous HSCT group. Five patients experienced secondary malignancies (leukemia, myelodysplastic syndrome, low malignant sarcoma, and pheochromocytoma) with 3 of those malignancies occurring in the autologous HSCT group and 2 occurring in the maintenance therapy group. There was a total of 27 late deaths (n=15 autologous HSCT; n=12 maintenance therapy) with most late deaths occurring because of a tumor. Overall results of this study showed that HDT with autologous HSCT was superior to maintenance therapy at improving EFS; however, researchers noted limitations of this study included the low compliance with the randomization results and the influence of the treatment of subsequent recurrences on the proportions of OS.

Wilms Tumor

Spreafico et al. (2020) examined data on subgroups of patients with Wilms tumor, in particular those who suffer from relapse. Patient treatment plans that included HDT with autologous HSCT were analyzed. Data from the European Blood and Marrow Transplantation Registry included children (n=69) receiving autologous HSCT as consolidation of first or second remission (after first relapse). Different HDT regimens were administered – most with either melphalan-containing (n = 34) or thiotepa-containing (n = 14). For the total population, the 5-year OS and EFS probabilities were 0.67 and 0.63, respectively and included a median observation time of 7.8 years); for children transplanted in first remission, OS and EFS were 0.69 and 0.72. Using a given pretransplant regimen (e.g., melphalan alone versus regimens with multiple drugs) did not appear to influence OS and EFS probability after autologous HSCT, but significantly influenced platelet engraftment (more delayed with thiotepa).

Delafoy et al. (2022) conducted a retrospective data analysis on 54 patients who received HDT + autologous HSCT for Wilms tumors between the years 2000 – 2016. Of the 54 patients there were 13 were treated with HDT + HSCT as first line and 41 were treated due to recurrence/relapse. The selection criteria applied for patient eligibility for HDT + HSCT matched the current criteria stipulated in the International Society of Pediatric Oncology (SIOP) UMBRELLA protocol. The objective response rate to HDT was 21%, with a disease control rate after HDT of 85%. Main nonhematological acute grades 3-4 toxicities were digestive and renal with no significant difference of toxicity rate observed between HDT regimens and schedules. There were three deaths reported, two patients shortly after receiving autologous HSCT due to renal and multiorgan failure respectively, and one heavily pretreated patient died of late respiratory failure. The objective response rate to HDT + HSCT was 21%, with a disease control rate after HDT + HSCT of 85%. After a median follow-up of 7 years, the 5-year EFS and OS were 54% (95% CI: 32%-76%) and 62% (95% CI: 31%-82%) for frontline patients, and 57% (95% CI: 39%-71%) and 69% (95% CI: 52%-81%) at recurrence.

Malogolowkin et al. (2017) described the outcomes of 253 patients with Wilms tumor who experienced relapse who received HDT followed by autologous HSCT. Data collected between 1990 and 2013 by the Center for International Blood and Marrow Transplantation Research was analyzed to suggest HDT followed by autologous HSCT for relapsed Wilms tumor is well tolerated and outcomes are similar to other reports in the medical literature. The 5-year estimates for EFS and OS were 36% and 45%, respectively. Relapse of primary disease was the cause of death in 81% of the population, with EFS, OS, relapse and transplant-related mortality showing no significant differences when broken down by disease status at transplant, time from diagnosis to transplant, year of transplant or conditioning regimen.

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National and Specialty Organizations

The **American Society for Transplantation and Cellular Therapy (ASTCT)** published *Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy* (Kanate et al. 2020) which stipulates the various indications and uses for autologous and allogeneic HSCT for different disease processes.

The **National Marrow Donor Program (NMDP)** has published the following guidance: *Disease-Specific HCT Indications and Outcomes Data; Engraftment; HLA Matching; Patient Eligibility for HCT; Transplant Consultation Timing; and Treatment Before Transplant* (¹⁻⁶ NMDP date unknown).

The **National Comprehensive Cancer Network (NCCN)** published the following *Clinical Practice Guidelines in Oncology*:

- Bone Cancer (v 2.2024)
- *Ovarian Cancer Continue Including Fallopian Tube Cancer and Primary Peritoneal Cancer (v 3.2024)* states “Any stage embryonal tumorii or Any stage endodermal sinus tumor (yolk sac tumor) or Stage II–IV dysgerminoma or Stage I, grade 2 or 3 or Stage II–IV immature teratoma or Any stage nongestational choriocarcinoma ... Persistently elevated markerskk with definitive residual disease [OR] Residual malignancy [consider] TIP (paclitaxel/ifosfamide/ cisplatin) or High-dose chemotherapyll + hematopoietic cell transplant (HCT) (strongly recommend referral to tertiary care center for potentially curative regimen)”
- *Testicular Cancer (v 1.2025)* states:
 - Second line chemotherapy regimens for metastatic germ cell tumors the preferred regimens are: “Carboplatin/etoposide Carboplatin 700 mg/m2 /day (body surface area) IV administered on days -5, -4, and -3 Etoposide 750 mg/m2 /day IV administered on days -5, -4, and -3 Administer days -5, -4, and -3 before peripheral blood stem cell infusion for 2 cycles” [OR] “Paclitaxel/ifosfamide/carboplatin/etoposide Paclitaxel 200 mg/m2 IV over 24 hours on Day 1 Ifosfamide 2000 mg/m2 over 4 hours with mesna protection on Days 2–4 Repeat every 14 days for 2 cycles followed by Carboplatin AUC 7–8 IV over 60 minutes on Days 1–3 Etoposide 400 mg/m2 IV on Days 1–3 Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles”
 - Third line systemic therapy regimens for metastatic germ cell tumors the preferred regimens are high-dose chemotherapy regimens: “Carboplatin/etoposide Carboplatin 700 mg/m2 /day (body surface area) IV administered on days -5, -4, and -3 Etoposide 750 mg/m2 /day IV administered on days -5, -4, and -3 Administered days -5, -4, and -3 before peripheral blood stem cell infusion for 2 cycles” [OR] “Paclitaxel/ifosfamide/carboplatin/etoposide Paclitaxel 200 mg/m2 IV over 24 hours on Day 1 Ifosfamide 2000 mg/m2 over 4 hours with mesna protection on Days 2–4 Repeat every 14 days for 2 cycles followed by Carboplatin AUC 7–8 IV over 60 minutes on Days 1–3 Etoposide 400 mg/m2 IV on Days 1–3 Administered with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles”
- Neuroblastoma (v 1.2024)
- Wilms Tumor (Nephroblastoma) (v 1.2023)

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
	Collection Codes
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services

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38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions
38243	Hematopoietic progenitor cell (HPC); HPC boost

HPCPS (Healthcare Common Procedure Coding System)

Code	Description
S2140	Cord blood harvesting for transplantation, allogeneic
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 pheresis 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

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

- 02/12/2025** Policy revised to allow tandem or sequential HSCT for any primary malignant germ cell tumors. Full annual review will remain scheduled for June 2025.
- 06/12/2024** New policy comprised of retired MCPs 272 (Ewing's), 194 (Germ Cell), 193 (Neuroblastoma), and 283 (Wilms) to condense HSCT for Solid Tumors. IRO Peer Reviewed on May 28, 2024, by a practicing physician board certified in Internal Medicine and Medical Oncology.

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