This Medical Guidance is intended to facilitate the Utilization Management process. 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 (i.e., 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 exclusions 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 following website: http://www.cms.hhs.gov/center/coverage.asp.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does have a NCD called Stem Cell Transplantation (110.8.1) and autologous HSCT is covered for the treatment of recurrent or refractory neuroblastoma.¹

INITIAL COVERAGE CRITERIA

All transplants must be approved by the Medical Director prior to authorization

Members must meet the criteria outlined below for transplantation and the diagnosis must be made by a Hematologist, Oncologist and/or transplant surgeon.

Pre-Transplant Evaluation:

1. General requirements for transplant evaluation include all of the following:² ³ ⁹ ¹²
   - History and physical examination
   - **Psychosocial evaluation and clearance**: This must be completed and documentation submitted for review before any additional transplant work-up or testing is initiated.
   - Dietary consult and clearance for transplant
   - Disease evaluation may include all the following:
     - Bone marrow biopsy and/or bone marrow aspiration: must show adequate response to therapy
     - CT scan
- PET scan
- Cardiac Echocardiogram: Ejection fraction > 50%
- EKG
- Chest X-ray
- Performance Status: [ONE]
  - *Karnofsky score 70-100%
  - **Eastern Cooperative Oncology Group (ECOG) grade 0-2
- Neurological exam and clearance for transplant: [ONE]
  - Normal exam by H&P
  - Abnormal neurological exam with positive findings: [ONE]
    - Lumbar puncture normal cytology
    - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- Pulmonary function testing: [ALL]
  - diffusion capacity (DLCO) > 60%
  - forced expiratory volume (FEV) > 60%
  - forced capacity (FVC) > 60%
- Lab studies:
  - Complete blood cell count, liver function tests, kidney profile, coagulation profile
    - prothrombin time, partial thromboplastin time
    - SGOT or SGPT > 2x upper limit of normal
  - HIV testing
  - Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis D, Ebstein-Barr virus (EBV), cytomegalovirus (CMV) serology, syphilis, toxoplasmosis, herpes simplex virus
  - HLA Antibody
  - Blood type
  - Serum creatinine: <1.5mg%
  - creatinine clearance: > 60 ml/min
  - Bilirubin < 2mg%

Within the last 12 months the following is required:

- Colonoscopy (indicated > age 50 with removal of any polyps if applicable)
- Dental examination (contact plan for coverage criteria)
- GYN examination with Pap smear (indicated > age 18) with complete workup and treatment of abnormal results as indicated
- Mammogram (indicated > age 40) with complete workup and treatment of abnormal results as indicated
- Osteoporosis screening with DEXA scan: [ONE]
  - cholestatic disorders
  - prolonged corticosteroid therapy
postmenopausal women
age > 65

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<tr>
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<tbody>
<tr>
<td>Able to carry on normal activity, no evidence of disease</td>
</tr>
<tr>
<td>Able to carry on normal activity, minor signs or symptoms of disease</td>
</tr>
<tr>
<td>Normal activity with effort, some signs and symptoms of disease</td>
</tr>
<tr>
<td>Cares for self, unable to carry on normal activity or to work</td>
</tr>
<tr>
<td>Requires occasional assistance from others but able to care for most needs</td>
</tr>
<tr>
<td>Requires considerable assistance from others and frequent medical care</td>
</tr>
<tr>
<td>Disabled, requires special care and assistance</td>
</tr>
<tr>
<td>Severely disabled, hospitalization indicated, death not imminent</td>
</tr>
<tr>
<td>Very sick, hospitalization indicated, active support treatment necessary</td>
</tr>
<tr>
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<td>Dead</td>
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</table>

<table>
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<tr>
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<tbody>
<tr>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
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<tr>
<td>Dead</td>
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</tbody>
</table>

Criteria for Hematopoietic Autologous Stem Cell transplantation (HSCT) Transplantation:

1. **Hematopoietic Autologous stem-cell transplantation (HSCT)** may be considered medically necessary and may be authorized for the treatment of high risk neuroblastoma when the following criteria are met:

- **Single** autologous hematopoietic stem-cell transplantation may be considered medically necessary
  - For initial treatment when any of the following are present: [ONE]
    - age older than 1 year; or
    - disseminated disease; or
    - MYCN oncogene amplification; or
    - unfavorable histopathologic findings
  - For recurrent or refractory neuroblastoma: [ONE]
    - Relapse is defined as tumor recurrence after a prior complete response; or

Page 3 of 12
Primary refractory disease is defined as a tumor that does not achieve a complete remission after initial standard-dose chemotherapy.

- A repeat autologous hematopoietic stem cell transplantation may be considered medically necessary for either of the following: [ONE]
  - primary graft failure; or
  - failure to engraft

  **AND**

- No absolute contraindications:
  - Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
  - Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
  - Irreversible brain damage or active central nervous system disease
  - Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
  - No behavioral health disorder by history or psychosocial issues: [One]
    - if history of behavioral health disorder, no severe psychosis or personality disorder
    - mood/anxiety disorder must be excluded or treated
    - member has understanding of surgical risk and post procedure compliance and follow-up required

  **Note:** Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

  - No adequate social/family support

**CONTINUATION OF THERAPY**

A review for any stem cell transplantation procedure is valid for one year from the time the request was approved. Due to potential lengthy organ donor waiting time, an annual review of clinical information should be conducted to evaluate any changes in the member’s clinical status.

**COVERAGE EXCLUSIONS**

1. Autologous HSCT when the above criteria are not met
2. Autologous HSCT when used as initial treatment of low or intermediate-risk neuroblastoma
3. Tandem autologous HSCT is considered investigational to treat neuroblastoma as the evidence is insufficient
4. Allogeneic HSCT is considered investigational to treat neuroblastoma as the evidence is insufficient.
5. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered.
6. The following absolute contraindications to stem cell transplantation are not covered:
   - Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
   - Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
   - Irreversible brain damage or active central nervous system disease
   - Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
   - No behavioral health disorder by history or psychosocial issues: [One]
     - if history of behavioral health disorder, no severe psychosis or personality disorder
     - mood/anxiety disorder must be excluded or treated
     - member has understanding of surgical risk and post procedure compliance and follow-up required

   **Note:** Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

   - No adequate social/family support

7. Relative contraindications to stem cell transplantation include all of the following:
   - poor cardiac function (ejection fraction < 50%)
   - poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to AML
   - poor renal function (creatinine clearance < 60ml/min)
   - poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
   - active central nervous system involvement
   - presence of human immunodeficiency virus (HIV)
   - an active infection with any ONE of the following:
     - hepatitis B virus (HBV)
     - hepatitis C virus (HCV)
     - human T-cell lymphotropic virus (HTLV)-1
   - Karnofsky rating <70% ; OR
   - Eastern Cooperative Oncology Group (ECOG) performance status >2

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**DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL**

**Neuroblastoma**

Neuroblastoma is a type of cancer that arises in sympathetic nervous system tissue, mainly in the adrenal medulla. It largely affects infants and children with 90% of the cases diagnosed before the age of 5 years and it accounts for approximately 18% of pediatric cancers and 15% of pediatric cancer deaths. It is the most common extracranial solid tumor in children, with metastatic disease at diagnosis in half of the cases. The cause is
unknown, but because of the young age at onset, factors before conception and during gestation may be considered. Children with a localized, resectable neuroblastoma have the best prognosis and chance for long-term, disease-free survival. Infants 12 months or younger with advanced disease also have a good prognosis. Neuroblastoma most commonly presents as an abdominal mass and additional symptoms can be caused by the tumor pressing against other tissues or from metastasis to bone. Signs of neuroblastoma include a mass in the abdomen, neck, or chest; bone pain; abdominal pain; emesis; weight loss; anorexia; fatigue; bulging eyes; dark circles around the eyes; and weakness or paralysis. Infants can present with distended abdomen, difficulty breathing, and blue-colored masses under the skin.  

Prognostic markers are used to stratify risk and assign treatment. In addition to age at diagnosis, these include the clinical stage of disease, regional lymph node involvement, site of primary tumor, tumor histology and the presence of the MTCN oncogene. The risk-based neuroblastoma treatment plan was developed by the Children’s Oncology Group and is used together with the International Neuroblastoma Staging System (INSS) to define **high risk** patients with neuroblastoma in the following table:

<table>
<thead>
<tr>
<th><strong>INSS Stage</strong></th>
<th><strong>Age</strong></th>
<th><strong>MYCN Status</strong></th>
<th><strong>INPC Classification</strong></th>
<th><strong>DNA Ploidy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>2A/2B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥365 d–21 y</td>
<td>Amplified</td>
<td>Unfavorable</td>
<td>-</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;365 d</td>
<td>Amplified</td>
<td>Any</td>
<td>Any</td>
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<tr>
<td></td>
<td>≥365 d–21 y</td>
<td>Nonamplified</td>
<td>Unfavorable</td>
<td>-</td>
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<td></td>
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<td>Any</td>
<td>-</td>
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<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;365 d</td>
<td>Amplified</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>≥548 d–21 y</td>
<td>Any</td>
<td>Any</td>
<td>-</td>
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<td>&lt;365 d</td>
<td>Amplified</td>
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</tr>
</tbody>
</table>

**Key:**
*INPC = International Neuroblastoma Pathologic Classification; INSS = International Neuroblastoma Staging System.
**aDNA Ploidy: DNA Index (DI) > 1 is favorable, DI = 1 is unfavorable; hypodiploid tumors (with DI < 1) will be treated as a tumor with a DI > 1 (DI < 1 [hypodiploid] to be considered favorable ploidy).
**b**INSS stage 2A/2B symptomatic patients with spinal cord compression, neurologic deficits, or other symptoms are treated with immediate chemotherapy for four cycles. cINSS stage 3 or stage 4 patients with clinical symptoms as listed above receive immediate chemotherapy.

The INSS<sup>3</sup> stages based on clinical, radiologic and surgical evaluation are:

- Stage 1: localized tumor with complete gross excision and/or microscopic residual disease, ipsilateral lymph nodes negative for tumor (lymph nodes attached to and removed with tumor may be positive)
- Stage 2A: localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
Stage 2B: localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically
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 (unresectable) or by lymph node involvement
Stage 4: any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organ (except as defined by 4S)
Stage 4S: localized primary tumor (as defined for stage 1, 2A, or 2B) in infants aged less than one year with dissemination limited to skin, liver, or bone marrow (marrow involvement should be minimal)

Stem Cell Transplantation
Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person’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. Matching is performed on the basis of variability at three or more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

Pretransplant Evaluation
The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.

GENERAL INFORMATION

Summary of Medical Evidence
The evidence is sufficient and supports the safety and effectiveness of autologous hematopoietic stem-cell transplantation (auHSCT) as a component of the standard of care for the treatment of selected individuals with high-risk neuroblastoma.

**Cochrane**

A Cochrane review (2013) assessed high-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Three RCT’s including 739 children were identified. They all used an age of one year as the cut-off point for pre-treatment risk stratification. There was a statistically significant difference in event-free survival in favor of myeloablative therapy over conventional chemotherapy or no further treatment (3 studies, 739 patients; HR 0.78, 95% CI 0.67 to 0.90). There was a statistically significant difference in overall survival in favor of myeloablative therapy over conventional chemotherapy or no further treatment (2 studies, 360 patients; HR 0.74, 95% CI 0.57 to 0.98). However, when additional follow-up data were included in the analyses the difference in event-free survival remained statistically significant (3 studies, 739 patients; HR 0.79, 95% CI 0.70 to 0.90), but the difference in overall survival was no longer statistically significant (2 studies, 360 patients; HR 0.86, 95% CI 0.73 to 1.01). According to the authors, based on the currently available evidence, myeloablative therapy seems to work in terms of event-free survival however no conclusions can be made regarding the best treatment strategy. 29

**Single auHSCT:**

A large RCT by Berthold et al. (2005) 14 randomized 295 patients to receive either high-dose chemotherapy with autologous HSCT or conventional chemotherapy. Children who received high-dose therapy with autologous hematopoietic stem-cell transplantation had significantly improved three-year overall survival (OS) compared with those who received conventional therapy (66% versus 52%, respectively), as well as a significant improvement in three-year event-free survival (EFS) (53% versus 30%, respectively). Another more recent RCT by Kreissman (2013) showed that immunomagnetic purging of peripheral blood stem cells does not appear to improve survival in children and young adults with high-risk neuroblastoma receiving autologous stem cell transplant. Non-purged PBSC are acceptable for support of myeloablative therapy of high-risk neuroblastoma. 30 Additionally, several large prospective series and retrospective studies suggest improved outcomes with overall survival (OS) rates of 29%-37%. 15-19 High-dose chemotherapy and surgery have been shown to achieve minimal disease states in more than 50% of patients. Consolidation therapy, consisting of myeloablative therapy with autologous hematopoietic stem-cell transplantation rescue, results in 30–83% long-term disease-free survival. 20-21

**Tandem auHSCT:**

The evidence is not sufficient to allow conclusions about the clinical effectiveness and safety of tandem auHSCT as there are no large randomized controlled trials comparing single versus tandem transplants. Trials comparing single versus tandem HDC and PBSC therapy are needed to determine the clinical effectiveness and long-term safety of the intensified therapy in terms of improved survival rates, reduced incidence of disease recurrence, and possibly a decrease in mortality due to toxicity. The results of several relevant case series and two single arm series are summarized below.
A small single arm study of tandem high dose chemotherapy with stem cell rescue as consolidation for high risk neuroblastoma was conducted by Granger et al (2012) in the Children’s Oncology Group (COG). A total of 33 patients were enrolled. Twenty-two patients completed at least one HDC/SCR procedure and 17 patients completed both. The PFS of the 33 patients treated on this study is 24.2% ± 7.5% and OS is 36.4% ± 8.4% at 5 years. For patients who received at least one transplant PFS is 36.4% ± 11.0% and OS is 45.5% ± 11.2% at 5 years. Another small study by Seif et al (2013) was done to assess feasibility and toxicity of a tandem myeloablative regimen without total body irradiation (TBI) supported by autologous CD34 selected peripheral blood stem cells. Forty-one patients with high-risk neuroblastoma were enrolled; eight patients did not receive any myeloablative consolidation procedure, and seven received only one. From the time of study enrollment, the overall 3-year event-free survival (EFS) and overall survival (OS) were 44.8±9.6% and 59.2±9.2% (N=41). Several case series demonstrated outcomes for individuals with high-risk disease who received tandem autologous transplantation compared with single autologous transplantation. Three-year OS rates ranged from 57–79%. Sung et al. (2007) evaluated 52 patients > one year with newly diagnosed stage IV neuroblastoma who were assigned to receive tandem high-dose chemotherapy and autologous HSCT. Fifty patients received the first HSCT and 44 patients underwent a second HSCT with high-dose chemotherapy. Five-year OS and event-free survival (EFS) rates for the entire cohort were 64.3% and 62.1%, respectively. George et al. (2006) reported the outcomes of 97 patients with high-risk neuroblastoma who were treated with two consecutive courses of myeloablative therapy and autologous HSCT. Progression-free survival (PFS) at five and seven years from diagnosis was 47% and 45%, respectively. OS at five and seven years was 60% and 53%, respectively. Relapse occurred in 42% of patients, mainly within three years of transplantation and in primarily diffuse osseous sites.

Professional Organizations

According to the National Cancer Institute (NCI) Neuroblastoma Treatment PDQ 2014, treatment is stratified according to the following tumor risk:

- For low-risk tumors the approach is either observation or surgery and chemotherapy with or without surgery is recommended for symptomatic disease or unresectable progressive disease after surgery.
- For intermediate-risk tumors, chemotherapy is usually done before surgery and in infants surgery and observation is recommended.
- For high-risk patients the treatment regime includes chemotherapy, surgery, radiation therapy, hematopoietic stem cell transplantation, and immunotherapy.

**Coding Information:** The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

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<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
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<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>HCPCS</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood derived stem-cell transplantation, allogeneic</td>
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<tr>
<td>S2150</td>
<td>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</td>
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**Resource References**