Subject: Stem Cell Transplantation in Pediatric Patients

Policy Number: NMP250

Effective Date*: December 2005

Updated: January 2016

This National Medical Policy is subject to the terms in the IMPORTANT NOTICE at the end of this document

For Medicaid Plans: Please refer to the appropriate State’s Medicaid manual(s), publication(s), citation(s), and documented guidance for coverage criteria and benefit guidelines prior to applying Health Net Medical Policies

The Centers for Medicare & Medicaid Services (CMS)
For Medicare Advantage members please refer to the following for coverage guidelines first:

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<td></td>
<td>National Coverage Manual Citation</td>
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Instructions
- Medicare NCDs and National Coverage Manuals apply to ALL Medicare members in ALL regions.
- Medicare LCDs and Articles apply to members in specific regions. To access your specific region, select the link provided under “Reference/Website” and follow the search instructions. Enter the topic and your specific state to find the coverage determinations for your region. *Note: Health Net must follow local coverage determinations (LCDs) of Medicare Administration Contractors (MACs) located outside their service area when those MACs have exclusive coverage of an item or service. (CMS Manual Chapter 4 Section 90.2)
- If more than one source is checked, you need to access all sources as, on occasion, an LCD or article contains additional coverage information than contained in the NCD or National Coverage Manual.
- If there is no NCD, National Coverage Manual or region specific LCD/Article, follow the Health Net Hierarchy of Medical Resources for guidance.
Current Policy Statement
Health Net, Inc. considers pediatric high dose chemotherapy and stem cell transplantation in patients < 18 years of age medically necessary according to the following:

Note: Disease descriptions can be accessed through the National Cancer Institute Web site under "Types of Cancer"

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| Transplantation Of Cord Blood Stem Cells |

| Retransplantation |

**Pediatric Autologous Stem Cell Transplant**

**Hodgkin’s Disease**

Medically Necessary

Autologous transplantation is preferred for advanced Hodgkin’s Lymphoma (HL) or Hodgkin’s Disease (HD) (stage III or IV) that either fails to achieve a complete response* with primary chemotherapy and/or radiotherapy, or disease that relapses after an initial complete response using chemotherapy and/or radiotherapy.

Allogeneic transplantation should only be used for patients for whom autologous transplant is not feasible (e.g., extensive involvement of bone marrow).

*Responsiveness is defined as a tumor demonstrating either a complete or partial remission. Partial remission (response) is defined as at least a 50 % decrease in tumor burden.

**Investigational**

1. Initial or upfront therapy or for consolidation of patients in first complete remission
2. Salvage high dose chemotherapy/allogeneic bone marrow or peripheral stem cell (HDC/AlloSCS) for relapse* of HL/HD after high dose chemotherapy/autologous bone marrow or peripheral stem cell transplant.
3. Tandem or sequential transplants for the treatment of HL/HD
4. Patients with Small Lymphocytic Lymphoma (SLL)

* Relapse is the reappearance of disease in regions of prior disease (recurrence) and/or in new regions (extension) after initial therapy and attainment of complete response.
### Non-Hodgkin’s Lymphoma

**Medically Necessary**

1. Autologous transplantation is preferred for high-grade disease (lymphoblastic lymphoma, Burkitts lymphoma, diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, MALT lymphoma) in a patient with any of the following:
   - Refractory to primary, combination chemotherapy
   - In second or subsequent clinical remission
   - Chemotherapy sensitive, but only partial remission
   - Refractory relapsed disease (having first achieved a complete remission, relapsed, and achieved less than a complete remission with salvage therapy).

**Note:** Allogeneic transplantation may be preferable when the disease has spread to the bone marrow.

### Investigational

1. Small lymphocytic lymphoma (SLL)
2. Chronic lymphocytic lymphoma (CLL)
3. Primary therapy with evidence of low-grade histology
4. Initial therapy for all other subgroups of NHL
5. Autologous tandem transplant as there is not enough scientific evidence to show that this procedure prolongs survival compared to standard chemotherapy.
**Neuroblastoma**

**Medically Necessary**

Autologous transplantation is preferred when any of the following are met:

For treatment of high-risk neuroblastoma* (see below for classification) when both of the following are met:

- Patient does not have a concurrent condition/disease, which would seriously compromise the chance of attaining a durable complete remission with this therapy; and
- Patient has stem cell product that meets infusion criteria of viability and neuroblastoma stem cell contamination (i.e., less than 1 neuroblastoma cell per 100,000 peripheral blood progenitor cells or less than 10% morphological evidence bone marrow involvement) prior to transplant

AND

any of the following is met:

- In second complete remission
- As primary treatment for persons in Stage II to Stage III neuroblastoma when associated with more than 10 copies of the n-myc oncogene, regardless of age or stage of disease; or
- As primary treatment for persons in Stage IV neuroblastoma; or
- As therapy for primary recurrent or refractory disease with only a partial response when further treatment with a conventional-dose therapy is unlikely to attain a durable remission.

**Note:** Health Net, Inc. considers a repeat allogeneic or autologous bone marrow transplant medically necessary for persons with chemosensitive disease who have relapsed after an autologous or allogeneic stem cell transplant.

High-risk neuroblastoma is defined as any one of the following:

- Stage IV disease with either of the following:
  - Infants less than 1 year of age with amplified n-myc status of > 10 copies of the n-mvc gene, a powerful prognostic indicator in the childhood neuroblastoma; or
  - Greater than 1 year of age at diagnosis; or
- Stage IVS** disease in infants less than 1 year of age with amplified n-myc status of > 10 copies of the n-mvc gene; or
- Stage III disease with any of the following:
  - Amplified n-myc status of > 10 copies of the n-mvc gene; or
  - Elevated serum ferritin (> 142 ng/ml by radioimmunoassay or positive by counterimmunoelectrophoresis); or
  - Unfavorable histology; or
  - Stage IIA or IIB disease, in persons between ages 1 and 21 years, with amplified n-myc status of > 10 copies of the n-mvc gene and unfavorable histopathology by the Shimada classification.

** Stage IVS neuroblastoma is called "special" neuroblastoma because it is treated differently. The cancer is localized, with spread limited to liver, skin, and/or, to a very limited extent, bone marrow.

Tandem or sequential transplant for the treatment of patients with high-risk neuroblastoma

**Investigational**

1. High-grade glial tumors of the brain in adults

**Germ Cell Tumors**

**Medically Necessary**
Autologous stem cell transplant is medically necessary in the rare patient < 18 years of age for any of the following:

1. Germ cell tumors of the ovary for any of the following:
   - Relapsed germ cell tumors of the ovary that were responsive to standard chemotherapy
   - As consolidation therapy for patients with germ cell tumors of the ovary that is in complete remission
2. Germ cell tumors arising in testicular, mediastinal, retroperitoneal areas that are refractory to (less than 50% reduction in tumor burden) or exhibit only a partial response (at least a 50% reduction in tumor burden) to standard dose platinum chemotherapy
3. As consolidation therapy for persons with testicular cancer who relapse after an initial course of standard dose chemotherapy
4. Patients with germ cell tumors in second complete remission or second relapse following standard platinum-based chemotherapy
5. Tandem high dose chemotherapy (HDC) followed by autologous stem cell support for primary testicular cancer only, in patients who are in the first relapse or whose tumors are refractory to a cisplatin-based chemotherapeutic regimen

Investigational

1. As initial treatment (e.g., in lieu of an initial course of conventional platinum-based chemotherapy) of a poor risk germ cell tumor* or as a treatment following first relapse (e.g., in lieu of a course of conventional chemotherapy)
2. Tandem transplants for all other germ cell tumors except primary testicular cancer as above
3. For treatment of epithelial and mixed epithelial/germ cell ovarian cancers
4. Allogeneic stem cell transplant for the treatment of persons with germ cell tumors, including ovarian and testicular cancer

* Note: A poor risk germ cell tumor are not chemotherapy sensitive tumors or have a high tumor burden

Primitive Neuroectodermal Tumor (PNET) (Medulloblastoma)

Medically Necessary

1. Recurrent or refractory medulloblastoma and other PNETs, including:
   - Neuroblastoma arising in the central nervous system
   - Ependymoblastoma
   - Pinealblastoma

Investigational

1. Treatment for ependymoma

Ewing’s Sarcoma

Medically Necessary

1. Autologous transplantation preferred.
2. Recurrent or refractory Ewing’s sarcoma after chemotherapy / radiation therapy

Pediatric Allogeneic Stem Cell Transplant

Note: To simplify matters in allogeneic transplants, scientists have identified six human leukocyte antigen (HLA) markers to judge the quality of a match, i.e., the donor and recipient must be "compatible“. Since these antigen types are inherited, it is more likely that a relative (especially a sibling) is a 6/6 match than that a non-relative is a match. A six out of six (6/6) match between the donor and the patient is considered a "perfect" match. Obviously, a match on five out of the 6 HLA
markers is not quite as perfect, but sometimes there maybe no better solution than to go for a 5/6 HLA match.

### Acute Lymphoblastic / Lymphocytic Leukemia (ALL)

#### Medically Necessary

1. First choice is an HLA identical donor allogeneic transplant, after the first complete remission.

2. Stem cell transplant is the standard treatment for those with high-risk biological features, such as any of the following:
   - Philadelphia chromosome abnormality is present
   - Patients who achieve a first complete response and present with high risk disease as defined by hypoploidy with translocation at 9;22, 4;11, or 8;14, or high leucocyte white count >100,000/uL for ages 6-12 months or >50,000 for ages 10-20 years.
   - Patients who fail to achieve a complete response after 4 weeks of induction chemotherapy.
   - Patients who achieve a second complete response but relapse during therapy or < 1 year off therapy.
   - Patients who are in early relapse (i.e., > 5% blasts in the bone marrow and any blasts in the blood).
   - Extramedullary disease (disease outside the bone marrow, especially central nervous system)

**Note:** Allogeneic stem cell transplantation is used routinely, particularly for patients in second remission. The child who fails to enter initial or subsequent remission may benefit from allogeneic stem cell transplantation. Better results are obtained in earlier remissions than with multiple relapse or partial remissions.

**Note:** Bone marrow relapse is the principal form of treatment failure in ALL. The outlook for relapse after stem cell transplantation is poor. Remission can be obtained but the duration is short. Extramedullary relapse often precedes a bone marrow relapse. The most common sites of extramedullary spread are the CNS, testes, liver, kidneys, and spleen.

**Note:** Autologous stem cell transplant acceptable in patients with ALL in first or subsequent complete remission who have no human leukocyte antigens (HLA)-matched donor for allogeneic transplant.

#### Investigational

1. Initial therapy of ALL
2. Low grade lymphoma
3. Chronic Lymphocytic Leukemia (CLL) because there is not enough scientific evidence to show that this procedure prolongs survival compared to standard chemotherapy.
4. Small cell lymphocytic lymphoma
5. Tandem (or sequential) transplants for the treatment of ALL
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<th><strong>Acute Myelogenous Leukemia (AML)</strong></th>
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<td>Related allogeneic stem cell transplantation in first remission from a matched sibling donor is the standard treatment (around 50% of children are cured). For patients without a matched donor, allogeneic transplant from alternative donors is usually reserved for patients in first relapse. Allogeneic transplant has the lowest incidence of relapse, even compared to identical twin syngeneic transplant. Autologous stem cell transplantation has been utilized with AML patients who lack compatible donors when any of the following is met:</td>
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| 1. Patients who achieve a complete first response but do not have translocation at 8;21, 15;17, or 16q-.
2. Patients with high risk cytogenetic features (M7, M6, 5q-, Trisomy 8, Myelodysplastic presentation) or treatment induced AML.
3. Patients who relapse after continuation chemotherapy.
4. Patients who achieve a second or third complete response.
5. Patients who are in early relapse (i.e., 30% blasts in the blood & bone marrow). |
| *Sometimes called acute non-lymphocytic leukemia (ANLL)* |

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<td>Allogeneic transplantation in the first chronic phase or second chronic phase (following blast crisis) is preferred. Autologous and syngeneic stem cell transplantation have higher rates of relapse. Allogeneic stem cell transplantation patients who relapse may be appropriate for a second stem cell transplantation but survival rate is poor and complication rate higher. Relapsed CML may be restored to complete cytogenetic remission by IFN-alpha with leukocyte transfusions from the donor or by use of leukocyte infusions alone. Allogeneic stem cell transplantation is the treatment of choice for Juvenile Chronic Myelocytic Leukemia (JCML) when a donor can be found, but the incidence of relapse is high.</td>
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<thead>
<tr>
<th><strong>Investigational</strong></th>
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| 1. Autologous transplant for the treatment of chronic myelogenous leukemia (CML)
2. Salvage high dose chemotherapy with allogeneic stem-cell support (HDC/AlloSCS) for relapse of incomplete remission after high dose chemotherapy with autologous stem-cell support for patients with ALL and AML |
### Aplastic Anemia
(includes Fanconi’s anemia, red cell aplasia (Diamond-Blackfan syndrome), paroxysmal nocturnal hemoglobinuria, amegakaryocytic thrombocytopenia)

**Medically Necessary**

Long term survival for individuals with a matched sibling donor is higher than for those with unrelated donors. Allogeneic transplant from an unrelated donor should be reserved for those who fail alternative treatment, such as one course of immunosuppressive therapy*. Poor outcomes associated with history of numerous blood product transfusions.

Stem cell transplant indicated when all of the following criteria are met:

1. Child has severe aplastic anemia* defined as having at least three of the following:
   - Absolute neutrophil count < 500/mm$^3$
   - Platelets < 20,000/mm$^3$
   - Reticulocyte count < 1%
   - Bone marrow cellularity < 20%; and
2. If patient fails antithymocyte globulin (ATG) therapy, patient must have 6 of 6 HLA-matched related or unrelated donor, or 5 of 6 antigen matched family patient donor

* Note: For children < 20 years of age, one course of immunosuppressive therapy (IST) must have been tried.

**Investigational**

1. Polycythemia vera

### Sickle Cell Anemia

**Medically Necessary**

Allogeneic transplant preferred when all of the following criteria are met:

1. Children and young adults (≤ 25 years of age) who have an HLA-matched, related donor, preferably a matched sibling
2. Documented homozygous sickle cell anemia
3. Who have one or more of the following features associated with increased risk of stroke or end-organ damage:
   - Prior stroke (CVA)
   - Recurrent chest syndrome
   - Recurrent vaso-occlusive ("pain") crises
   - Red blood cell alloimmunization on chronic transfusion therapy

**Investigational**

- Sickle cell trait
- Transplant donor who is not HLA-identical
## Thalassemia Major

### Medically Necessary

1. Allogeneic transplant with homozygous beta-thalassemia (Cooley anemia, Thalassemia Major) in children and young adults ≤ 30 years of age when all of the following criteria are met:

   - Patient shows deterioration with conventional treatments including transfusions, splenectomy, and deferoxamine; and
   - Patient has minimal hepatomegaly, portal fibrosis, and active hepatitis; and
   - Has a suitable related or unrelated donor (5/6 HLA antigen match acceptable, HLA 6/6 antigen match preferred) – 4/6 HLA antigen match unrelated cord blood unit with adequate cell dose is acceptable

   **Note**: Transplantation is curative and should be performed before advanced disease develops.

### Investigational

- Autologous transplantation is not appropriate.
- Type and subtypes of thalassemia other than homozygous beta-thalassemia (Cooley anemia, Thalassemia Major)

### Storage Diseases (Mucopolysaccharidosis)

- (X-linked adrenoleukodystrophy, infantile metachromatic leukodystrophy, globoid cell leukodystrophy, Hurler syndrome, Gaucher’s disease, Maroteaux-Lamy)

### Medically Necessary

Allogeneic stem cell transplant when all of the following are met:

1. Patient is neurologically intact or minimal neurologic damage has occurred; and
2. Failed conventional therapy (such as diet modification or enzyme therapy); and
3. Using a 5/6 or 6/6 antigen matched, HLA molecular typing negative family patient donor - 4/6 HLA antigen match unrelated cord blood unit with adequate cell dose is acceptable
Investigational
1. Sanfilippo
2. Hunter syndrome

Severe Combined Immunodeficiency (SCID) Disorders
Wiskott-Aldrich Syndrome, DiGeorge syndrome, Infantile Malignant Osteopetrosis, Albers-Schonberg Disease (also known as marble bone disease), Kostmann’s Syndrome (severe infantile agranulocytosis), Leukocyte adherence deficiency, Familial erythrophagocytic lymphohistiocytosis

Medically Necessary
Allogeneic transplantation has been curative in some patients with infantile malignant osteopetrosis.

For Wiskott - Aldrich Syndrome:
1. Allogeneic transplantation from a matched sibling is the treatment of choice.
2. Allogeneic unrelated transplantation is under investigation.
3. Transplantation corrects all problems and abnormalities except thrombocytopenia.

For all diseases in children:
Treatment of choice using a 6/6 antigen matched, HLA molecular typing negative related or unrelated donor - when an HLA-identical sibling is available as a donor for a child recognized to have any of these lethal disorders, allogeneic bone marrow transplantation is the treatment of choice. Unfortunately, such donors are often not available. In their absence, the use of T-cell-depleted marrow from partly HLA-matched, related donors or from HLA-matched, unrelated donors has been successful. Using 4/6 HLA antigen match unrelated cord blood unit with adequate cell dose has also been successful.

Investigational
1. Chédiak-Higashi syndrome
2. Duncan syndrome
3. Neutrophil actin deficiencies

Transplantation Of Cord Blood Stem Cells
Health Net, Inc. considers transplantation of cord blood stem cells from related or unrelated donors medically necessary in pediatric patients in whom there is no other available stem-cell donor with the same or better matching characteristics and the cord blood is HLA mismatched at less than or equal to 2 antigen and with an adequate cell dose.

Note: Health Net, Inc. considers collection and storage of cord blood from a neonate medically necessary when an allogeneic transplant is imminent in an identified recipient with a diagnosis that is consistent with the need for allogeneic transplant.

Note: Health Net, Inc. does not consider prophylactic collection and storage of cord blood from a neonate for some unspecified future use as an autologous stem cell transplant in the original donor, or in case of a future need for allogeneic stem cell transplant in a related or unrelated recipient medically necessary.
Retransplantation

**Allogeneic - Related Donor**

Patients who have a related donor are eligible for a second allogeneic bone marrow transplant if they do not demonstrate evidence of engraftment, or if graft failure occurs due to rejection or graft versus host disease. Patients must not have evidence of overwhelming infection or end-stage organ dysfunction.

**Allogeneic - Unrelated Donor**

Patients who have an unrelated donor transplant are eligible for a second unrelated donor transplant if they meet all of the following:

1. Patients who demonstrate graft failure due to rejection or graft versus host disease (GVHD);
2. They are greater than six months from the first transplant, which included ablative chemotherapy alone or in combination with radiotherapy*;
3. Patients must have no evidence of major organ dysfunction and/or evidence of active infection.

Note: Retransplantation does not include infusion of donor leukocytes for persistent leukemia, which would need to be performed sooner than six months after the first transplant.

**Autologous**

Health Net Inc., does not consider second autologous transplants medically necessary for patients with recurrent disease.

Scientific Rationale – Update January 2016

Willard et al. (2014) completed a study in which the purpose was to examine the influence of age and conditioning with total-body irradiation (TBI) on the trajectory of cognitive functioning after treatment with pediatric hematopoietic stem-cell transplantation (SCT). Pediatric patients who were scheduled to undergo a stem cell transplant (SCT) were eligible for this study, with 315 patients completing a baseline assessment. Of these, 183 patients (58.1%) were alive at 1 year after SCT and completed additional assessments at 1, 3, and 5 years after SCT. Half of the long-term sample (52.1%) received TBI during conditioning. Cognitive functioning was assessed via age-appropriate standardized measures. At baseline, there were no differences in intelligence quotient (IQ) based on age. At 5 years after SCT, the youngest patients (<3 years old at baseline) who received TBI demonstrated a significantly lower IQ than those who did not receive TBI (P = .05). Longitudinal analyses (piecewise linear mixed-effects models with a knot at 1 year after SCT) revealed a significant impact of age and TBI over time. The youngest patients evidenced declines in cognitive functioning during the first year; however, patients who did not receive TBI largely recovered their functioning in subsequent years. In contrast, young patients who received TBI failed to recover the losses experienced during the first year after SCT, demonstrating stability in their functioning, but at a lower level. The findings clarify the relationship between TBI and age on cognitive outcomes in pediatric SCT survivors. Young patients who receive TBI may benefit from early intervention efforts to minimize cognitive losses during the first year after SCT and to maximize potential recovery.

Prais et al. (2014) Pulmonary complications following hematopoietic stem cell transplantation (HSCT) are common and often subclinical. Periodic pulmonary function testing (PFT) is mandatory. This study sought to evaluate the effectiveness of long-term PFT surveillance for children undergoing HSCT and identify potential risk factors. The authors reviewed long-term PFT for HSCT patients at a tertiary pediatric center. Inclusion criteria were PFT prior to and at least once following HSCT. Fifty-seven patients performed 202 spirometry and 193 plethysmographic maneuvers; 41 were tested during the first year after HSCT, but only 29 were
evaluated consistently long term (2-12 years). FVC and FEV(1) decreased gradually suggesting a restrictive ventilatory defect: FVC % predicted [mean±SD]dropped from 91±14% to 85±17% after 0-24 months and 80±19% beyond 2 years (P=0.01) whereas FEV(1) dropped from 95±16% to 88±19% and 82±20%, respectively (P=0.002). A slight reduction in TLC was observed. Those undergoing allogeneic HSCT had a greater decline in FVC (P=0.025) and FEV(1) (P=0.025) as did those conditioned with radiation, regarding both FVC (P=0.003) and FEV(1) (P=0.002). Decline occurred earlier (≤2 years) after chemotherapy compared with radiation. Seven children had severe irreversible obstruction at>2 years despite therapeutic intervention. Most survivors of childhood HSCT maintain almost normal pulmonary function although mild restrictive lung disease may develop, particularly following allogeneic HSCT and conditioning with radiation. Severe airways obstruction developed in a small minority. The surveillance protocol for PFT needs to be followed more stringently to enable intervention possibly before early subclinical changes progress and become irreversible.

Scientific Rationale – Update January 2015

Locatelli et al (2014) analyzed the outcome of 243 children with high-risk (HR) AML in first CR1 enrolled in the AIEOP-2002/01 protocol, who were given either allogeneic (ALLO; n=141) or autologous (AUTO; n=102) hematopoietic SCT (HSCT), depending on the availability of a HLA-compatible sibling. Infants, patients with AML-M7, or complex karyotype or those with FLT3-ITD, were eligible to be transplanted also from alternative donors. All patients received a myeloablative regimen combining BU, CHOP and BEAM; AUTO-HSCT patients received BM cells in most cases, while in children given ALLO-HSCT stem cell source was BM in 96, peripheral blood in 19 and cord blood in 26. With a median follow-up of 57 months (range 12-130), the probability of disease-free survival (DFS) was 73% and 63% in patients given either ALLO- or AUTO-HSCT, respectively (P=NS). Although the cumulative incidence (CI) of relapse was lower in ALLO- than in AUTO-HSCT recipients (17% vs 28%, respectively; P=0.043), the CI of TRM was 7% in both groups. Patients transplanted with unrelated donor cord blood had a remarkable 92.3% 8-year DFS probability. The authors concluded altogether, these data confirm that HSCT is a suitable option for preventing leukemia recurrence in HR children with CR1.

Zheng et al (2014) presented a clinical comparison of unrelated cord blood transplantation (CBT) and human leukocyte antigen (HLA)-matched sibling allogeneic peripheral blood stem cell or bone marrow transplantation (allo-PBSCT/BMT) in children with high-risk or advanced acute leukemia. A total of 115 consecutive pediatric patients received unrelated CBT (n=90) or sibling allo-PBSCT/BMT (n=25) between 2000 and 2012. Neutrophil and platelet recovery were significantly delayed after CBT compared to allo-PBSCT/BMT. There was no difference in the incidence of acute graft-versus-host disease (GVHD) or chronic GVHD between the two groups. The cumulative incidence of transplant-related mortality (TRM) was higher in the CBT group than in the allo-PBSCT/BMT group (32.5 vs 12.8 %) (p=0.03). The cumulative incidence of relapse was 13.1 % after CBT, which was significantly lower than that of after allo-PBSCT/BMT (45.3 %) (p=0.015). The overall survival (OS) and leukemia-free survival (LFS) in the CBT group were similar to those of the allo-PBSCT/BMT group; however, for acute myeloid leukemia (AML) patients, the 5-year LFS in the CBT group was slightly better than the allo-PBSCT/BMT group (55.7 % for CBT and 32.7 % for allo-PBSCT/BMT) (p=0.08). The authors concluded the comparisons suggest that for high-risk or advanced childhood acute leukemia, unrelated CBT has a higher TRM and similar long-term survival, but better antileukemia effect than HLA-matched sibling PBSCT/BMT. New strategies and better supportive care are required to decrease the TRM of CBT.
Wood et al (2014) reported adolescents and young adults (AYAs, ages 15 to 40 years) with cancer have not experienced survival improvements to the same extent as younger and older patients. They compared changes in survival after myeloablative allogeneic hematopoietic cell transplantation (HCT) for acute lymphoblastic leukemia (ALL) among children (n = 981), AYAs (n = 1218), and older adults (n = 469) who underwent transplantation over 3 time periods: 1990 to 1995, 1996 to 2001, and 2002 to 2007. Five-year survival varied inversely with age group. Survival improved over time in AYAs and paralleled that seen in children; however, overall survival did not change over time for older adults. Survival improvements were primarily related to lower rates of early treatment-related mortality in the most recent era. For all cohorts, relapse rates did not change over time. A subset of 222 AYAs between the ages of 15 and 25 at 46 pediatric or 49 adult centers were also analyzed to describe differences by center type. In this subgroup, there were differences in transplantation practices among pediatric and adult centers, although HCT outcomes did not differ by center type. Survival for AYAs undergoing myeloablative allogeneic HCT for ALL improved at a similar rate as survival for children.

**Scientific Rationale – Update January 2013**

Granger et al (2012) reported the results of this single arm trial of induction chemotherapy, local control measures (surgery and local radiation), and tandem high dose chemotherapy (HDC) with stem cell rescue (HDC/SCR). Patients with high risk neuroblastoma (NBL) underwent five cycles of induction chemotherapy and resection of primary tumors. Peripheral blood stem cells (PBSC) were collected after Course 3 without ex vivo manipulation. Myeloablative chemotherapy was performed in rapid sequence after induction chemotherapy and surgery. The ability of patients to complete both cycles of HDC/SCR was a primary endpoint. Transplant-related toxicity, progression-free survival (PFS) and overall survival (OS) were recorded. A total of 33 patients were enrolled. Twenty-two patients completed at least one HDC/SCR procedure and 17 patients completed both. Only one patient had insufficient stem cells collected for both transplants. There was one transplant-related death; engraftment was rapid and toxicity was as expected. 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. Investigators concluded the treatment of high risk NBL with tandem HDC/SCR is feasible in terms of transplant-related mortality and the ability to collect adequate PBSC for two transplants. The outcomes from this intensified treatment have been used to design a Children’s Oncology Group Phase III study testing the efficacy of tandem HDC/SCR.

Sung et al (2012) investigated 50 consecutive patients with high-risk neuroblastoma were assigned to receive tandem HDCT (high-dose chemotherapy)/auto-SCT after nine cycles of induction chemotherapy. CEC (carboplatine-toposide-cyclophosphamide) regimen and TM (thiotepa+melphalan)-TBI regimen (or TM regimen for stage 3 patients) were the first and second HDCT regimens. Local radiotherapy, differentiation therapy with 13-cis-retinoid acid and immunotherapy with interleukin-2 were given after tandem HDCT/auto-SCT. Of the 50 patients, 49 underwent a first HDCT/auto-SCT and 47 underwent a second HDCT/auto-SCT. The tumor relapsed or progressed in 14 patients, secondary malignancy developed in one patient and one patient died from chronic lung disease. Therefore, 34 patients remained event free with a median follow-up of 54.5 months (range, 14-94 months) from diagnosis. The probabilities of 5-year OS and EFS for all 50 patients were 77.0% and 71.4%, respectively. However, all patients who remained event free for >3 years after tandem HDCT/auto-SCT experienced late adverse effects. Chemotherapeutic dose-escalation strategy using tandem HDCT/auto-SCT was very encouraging for survival. Investigators noted further studies incorporating newer
treatment modalities are needed to reduce late adverse effects without jeopardizing the survival rate.

Hamidieh et al (2012) report our long-term results of HSCT in pediatric AML patients using non-total body irradiation conditioning regimen. From May 1991 to June 2010, 133 pediatric patients with AML (age<15 y) who were referred to the authors institute underwent autologous (auto-) or allogeneic (allo-) HSCT. The conditioning regimen consisted of oral busulfan plus etoposide in auto-HSCT patients and oral busulfan plus cyclophosphamide in allo-HSCT patients. Overall survival (OS), leukemia-free survival (LFS), probability of relapse, and transplantation-related mortality at 3 years were 67.6%, 62.2.5%, 27.3%, and 10.1%, respectively. There was no significant difference between allo-HSCT and auto-HSCT groups. In multivariable analysis using Cox proportional hazards regression model, male sex was associated with significantly improved OS and LFS. An age ≤3 years was associated with higher relapse and worse OS and LFS. Authors concluded the role of allo-HSCT in pediatric AML patients in first complete remission is uncertain. Further randomized studies are recommended to clarify the optimal postremission therapy in these patients.

Schechter et al (2012) sought to evaluate the outcome of second allogeneic HSCT for children with relapsed leukemia with focus on factors that potentially improve outcome. Thirty-eight children were identified. The median time between transplants was 18.6 months (range 6.7-50.1 months). With median follow-up of 44 months the 2-year overall survival (OS) was 59.1±8.2%. The leukemia-free survival was 51.8±8.2% and the non-relapse mortality 30.8±7.9%. Eleven patients (30%) died of non-relapse mortality at a median of 37 days (range 16-260 days) from second HSCT. Twenty-one patients developed acute graft-versus-host disease (aGVHD) after second HSCT. Patients who developed aGVHD had lower risk for mortality compared to patients who did not have aGVHD, with a hazard ratio (HR) of 0.27. Similarly, patients who developed aGVHD following second HSCT had lower risk for relapse. Patients who developed aGVHD after first HSCT were less likely to benefit from second HSCT compared to patients without aGVHD after first HSCT. The authors concluded that second HSCT for pediatric relapsed leukemia can result in acceptable survival and aGVHD is associated with improved outcome.

Lee et al (2012) identified significant prognostic variables for the survival rate for childhood acute lymphoblastic leukemia (ALL) by analyzing the outcomes of allogeneic HSCT in acute lymphoblastic leukemia ALL patients in second complete remission (CR). Fifty-three ALL patients (42 men, 79%) who received HSCT in second CR from August 1991 to February 2009 were included (26 sibling donor HSCTs, 49%; 42 bone marrow transplantations, 79%). Study endpoints included cumulative incidence of acute and chronic graft-versus-host disease (GVHD), relapse, 1-year transplant-related mortality (TRM), disease-free survival (DFS), and overall survival (OS). Cumulative incidences of acute GVHD (grade 2 or above) and chronic GVHD were 45.3% and 28.5%, respectively. The estimated 5-year DFS and OS for the cohort was 45.2±6.8% and 48.3±7%, respectively. Only donor type, i.e., sibling versus unrelated, showed significant correlation with DFS in multivariate analysis. The rates of relapse and 1 year TRM were 28.9±6.4% and 26.4±6.1%, respectively, and unrelated donor HSCT and HLA mismatch were significantly correlated with increased TRM in univariate analysis. Investigators concluded in this single institution study spanning more than 17 years, sibling donor HSCT was the only factor predicting a favorable result in multivariate analysis, possibly due to increased TRM resulting from unrelated donor HSCT.
**Scientific Rationale – Update March 2011**

van den Berg et al (2011) reported on the treatment of children and adolescents with acute lymphoblastic leukemia (ALL) in first relapse. The protocol focused on intensive chemotherapy preceding allogeneic stem cell transplantation (SCT) in early bone marrow relapse; rotational chemotherapy in late relapse, without donor; postponement of cerebro-spinal irradiation in late isolated CNS relapse; and treatment in very late bone marrow relapse with chemotherapy only. 158 pediatric patients with ALL in first relapse were recorded. Ninety-nine patients were eligible; 54 patients with early and 45 with late relapse. Eighteen patients had an isolated extra-medullary relapse; 69 patients had bone marrow involvement only. Five-years EFS rates for early and late relapses were 12% and 35%, respectively. For early relapses 5 years EFSs were 25% for patients transplanted; 0% for non-transplanted patients. For late relapses 5 years EFS was 64% for patients treated with chemotherapy only, and 16% for transplanted patients. For very late relapses EFS was 58%. The investigators concluded the data suggest the superiority of SCT for early relapse patients. For late relapses a better outcome is achieved with chemotherapy only using the rotational chemotherapy scheme. The most important factor for survival was interval between first CR and occurrence of the first relapse.

Caocci et al (2010) used child-self and parent-proxy reports to prospectively evaluate health related quality of life (HRQoL) in 28 beta-thalassemia children who underwent allogeneic HSCT. The PedsQL 4.0 Generic Core Scales were administered to patients and their parents 1 month before and 3, 6, 18 months after transplantation. Two-year overall survival, thalassemia-free survival, mortality and rejection were 89.3%, 78.6%, 10.9% and 14.3%, respectively. The cumulative incidence of acute and chronic graft-versus host disease (GVHD) was 36% and 18%, respectively. Physical functioning significantly declined from baseline at 3 months after HSCT. Major improvements were seen afterwards up to 18 months after HSCT. Agreement between child- and parent proxy-ratings was high. Chronic GVHD was the most significant factor associated with lower HRQoL scores over time. The investigators concluded the child-self and parent-proxy reports showed an improvement in the HRQoL of thalassemia children after HSCT. Overall, our study provides preliminary evidence-based data to further support clinical decision-making in this area.

Yalcin et al (2010) compared the effectiveness of myeloablative therapy with conventional therapy in children with high-risk neuroblastoma in a Cochrane review of randomized controlled trials (RCTs) comparing the effectiveness of myeloablative therapy with conventional therapy in high-risk neuroblastoma patients. Two authors independently performed study selection, data extraction and risk of bias assessment. When possible, results were pooled. Three RCTs including 739 children were identified. The meta-analysis of event-free survival showed a significant difference in favor of the myeloablative therapy group, as did the meta-analysis of overall survival. The meta-analysis of secondary malignant disease and treatment-related death did not show a significant difference between the treatment groups. In one study a significant difference in favor of the conventional therapy group was identified for renal effects, interstitial pneumonitis and veno-occlusive disease, whereas for serious infections and sepsis no significant difference between the treatment groups was identified. In the individual studies the authors evaluated different subgroups, but the results were not univocal in all studies. All studies had some methodological limitations. They concluded based on the currently available evidence, myeloablative therapy seems to be a good treatment option for children with high-risk neuroblastoma. It results in higher survival rates than conventional therapy, although possible higher levels of adverse effects should be kept in mind. A definitive conclusion regarding the effect of myeloablative therapy in different subgroups is not possible. They noted further this systematic review only allows a
conclusion on the concept of myeloablative therapy; no conclusions can be made regarding the best treatment strategy. Future trials on the use of myeloablative therapy for high-risk neuroblastoma should focus on identifying the most optimal induction and/or myeloablative regimen.

Scientific Rationale – Update January 2008
A Medline search was performed to review the current guidelines and to confirm if additional or revised criteria were applicable to this policy. There were no supplementary guidelines or position statements, relevant to this policy, found at this time.

Castagna et al. (2007) prospectively enrolled 32 patients with relapsed and refractory Hodgkin's disease (HD) to receive tandem high-dose chemotherapy and autologous hematopoietic stem-cell transplantation (HSCT). The median patient age was 31 years. Twenty-nine patients with chemosensitive disease after the initial induction period received high-dose melphalan and autologous HSCT; twenty-seven patients received the second high-dose regimen followed by autologous HSCT. In an intention-to-treat analysis, the overall response rate increased after each stage of therapy. After a median follow-up of 39 months, the three-year OS was 79%, while the three-year freedom from progression (FFP) rate was 63%. The authors noted that the number of patients included in the present study was too small to identify prognostic factors, and to draw reliable conclusions on the efficacy of the proposed protocol.

According to the National Cancer Institute (NCI, 2007), acute lymphocytic leukemia (ALL) is the most common cancer in children, representing 23% of cancer diagnoses among children younger than 15 years. The incidence of ALL is substantially higher for white children than for black children and is highest in Hispanic children—nearly 43 per million. Children with Down syndrome have an increased risk for developing ALL, with a median age of three to four years. It is thought that ALL in children may have a prenatal link. Data suggests that chromosomal abnormalities and T-cell receptor rearrangements specific to certain leukemic cells may be present in the blood at birth. Similarly, studies of identical twins having concordant leukemia support this theory.

According to the NCI (2007), Ewing tumors occur most frequently in adolescence, and account for 4% of all childhood and adolescent malignancies. ETB occurs most commonly in the long bones of the extremities and the flat bones, such as the pelvis and chest wall. Extraosseous Ewing tumor (EOE) and peripheral primitive neuroepithelioma (PNET) occur most commonly in the trunk of the body. Ewing Family of Tumors (EFT) are aggressive cancers and may metastasize to the lungs, other bones and bone marrow. The exact cause of these tumors is unknown.

Scientific Rationale – Initial
The goal of stem cell transplantation, or bone marrow transplantation (BMT), is to replace unhealthy or destroyed bone marrow stem cells with normal bone marrow stem cells following treatment with high doses of chemotherapy/radiotherapy that are necessary to kill the abnormal cells in the body. An understanding of the human leukocyte antigen (HLA) system for donor selection, immunosuppression for prevention and treatment of graft-versus-host disease (GVHD), and significant advances in infectious disease therapy and supportive care have made stem cell transplantation commonplace in the era of modern medicine. Nonetheless, there still are significant limitations that make stem cell transplantation a risky medical procedure.
A child can receive either an autologous or an allogeneic transplant. Autologous transplantation relies solely on dose intensity as a therapeutic modality. In an autologous transplant, the patient’s own hematopoietic cells are collected from the patient, processed in the laboratory, frozen and stored for future use. The stored stem cells, therefore, are protected from the toxic effects of the chemotherapy, which generally cause long-term myelosuppression or even permanent myeloablation. Once the chemotherapeutic agents are metabolized, the cryopreserved stem cells are reinfused into the transplant recipient and the original immune system and bone marrow function gradually is reconstituted.

Cryopreservation of stem cells often may not be required if the stem cell harvest is performed on the day of the planned infusion of the stem cells. There are no alloimmune effects of autologous stem cell transplantation; these effects are seen uniquely in allogeneic transplantation. Sometimes in autologous transplant the stem cells are treated with drugs in order to selectively kill or remove (purge) any remaining cancer cells that may be present. In an allogeneic transplant, marrow stem cells from a healthy donor are used to restore bone marrow after high dose chemotherapy/radiotherapy and the recipient is guaranteed to receive a stem cell product that is free of tumor cell contamination. Once the decision to use allogeneic stem cells is made, an appropriate donor must be identified. Donors are selected primarily based on HLA typing, although other factors, such as age, sex, parity, and cytomegalovirus (CMV) serostatus are considerations. When an acceptable related donor is unavailable, a suitable volunteer unrelated donor is identified through registries of volunteer donors, such as the National Marrow Donor Program.

There are several reasons for doing a bone marrow transplant:

- To provide normal bone marrow to a patient whose own bone marrow stem cells are abnormal or defective;
- To provide normal bone marrow to a patient whose own marrow has been destroyed by chemotherapy and radiation therapy in order to treat cancer;
- To provide normal bone marrow stem cells to a child with a genetic disease that affects all of the organs in the body.

Hematologic malignancy is the main clinical indication for hematopoietic stem cell transplantation. There are two major types of leukemias, acute and chronic. Acute leukemia may involve either lymphocytes (acute lymphoblastic leukemia or ALL) or myeloid cells (acute myelogenous leukemia or AML). There are many different types of ALL and AML depending on the particular cell that has become malignant.

Allogeneic transplantation is the therapy of choice for individuals who have relapsed or refractory AML or high-risk AML in first remission. The decision to use autologous stem cells is made based on the nature of the hematologic malignancy being treated and the stage of the malignancy. Autologous transplantation is used with curative intent in individuals who have non-Hodgkin's lymphoma or Hodgkin's disease in second remission. Advanced lymphoid malignancies, including Hodgkin's and non-Hodgkin's lymphomas and chronic lymphocytic leukemia, often are treated with allogeneic transplantation after failure of a prior autologous procedure or earlier, in the case of advanced chemorefractory disease.

Chronic leukemia primarily affects the myeloid cells in the bone marrow (chronic myelogenous leukemia or CML) and is more commonly found in adults, although children and teenagers can also sometimes develop CML. In treating these children, allogeneic transplantation has an advantage over autologous transplantation as it provides a "graft versus leukemia effect", i.e., another person's healthy bone marrow kills residual leukemia cells and decreases the chance of relapse in the recipient. The disadvantage of allogeneic bone marrow stem cell transplantation is the risk of "graft
versus host disease" (or graft-versus-tumor effect), i.e., another person's T-cells attacks the recipient's body and causes a disease that affects skin, liver, gut and many other organs, requiring therapy with immunosuppressive drugs. If a matched related donor is available, such as brothers, sisters or occasionally parents, a stem cell transplant is indicated for high risk leukemia patients in first remission (such as acute myelogenous leukemia, Philadelphia chromosome positive acute lymphoblastic leukemia, and leukemia in infants) and for many children with acute leukemias whose leukemia has relapsed once the leukemia is in remission (i.e., no leukemia is seen in the bone marrow) with chemotherapy. Matched unrelated donors may also include umbilical cord blood. Children with chronic myelogenous leukemia who cannot be put into complete remission with drugs such as Gleevec, should undergo a transplant from a related or unrelated donor as early as possible in the course of the disease.

Transplantation is a potentially life-saving treatment for children with certain tumors, severe immunodeficiency diseases (e.g., Wiskott-Aldrich syndrome), aplastic anemia, inherited diseases of the bone marrow such as sickle cell anemia and thalassemia major where only the marrow stem cells are affected. For many patients with marrow failure syndromes including primary red cell aplasia, severe congenital neutropenia (Kostmann's syndrome), red cell aplasia (Diamond-Blackfan syndrome), amegakaryocytic thrombocytopenia, or severe aplastic anemia who have an HLA closely-matched related donor or who fail immunosuppressive chemotherapy, an allogeneic bone marrow transplant can result in 80-90% disease free survival. Seventy-five to 90% of children with thalassemia major or sickle cell disease who have an HLA matched relative can be cured of their hemoglobinopathy with a stem cell transplant. Finally, for children with most inherited severe immunodeficiency diseases, the only known cure and, therefore, the treatment of choice is an allogeneic bone marrow transplant in which up to 90% may be cured.

Although great strides have been made in the cure of many pediatric tumors, a subset of solid tumors remains for which the chance of survival remains uniformly poor. The probability of achieving disease-free survival for children with newly diagnosed metastatic rhabdomyosarcoma, Ewing's/PNET, or high-grade glioma remains less than 25%, despite multi-modal conventional therapy. Likewise, the survival from a variety of pediatric solid tumors and brain tumors such as medulloblastoma, which have proven resistant to or have recurred following conventional multi-modal therapy remains poor with less than 10% of patients achieving long-term survival.Autologous bone marrow stem cell transplants have been utilized as the final stage of therapy for these pediatric patients with some encouraging improvement in survival. Nonetheless, at least half of the patients develop recurrent disease. A principal barrier to survival is the development of tumor resistance to standard chemotherapy drugs.

Neuroblastoma is one of the most common types of solid tumors in childhood. While many children with neuroblastoma may be cured with surgical removal of the tumor and chemotherapy treatments, those with extensive disease and/or features that indicate a very high likelihood of recurrence (often referred to as high risk) may not respond as well to this standard therapy. In these patients, autologous bone marrow stem cell transplantation is used to treat these children. In this type of transplant, high dose chemotherapy used during a conditioning period is given to kill the tumor. Bone marrow function is then restored by infusing the patient’s own previously-stored bone marrow cells. One advantage to this approach is that the risk of graft versus host disease is eliminated. Because the majority of these children have neuroblastoma cells in their bone marrow, the stem cell collection should be purged of cancer cells before re-infusion by storing them in liquid nitrogen. More recently, this purging technique has been adapted to treat circulating bone marrow stem cells
in the blood that have been collected by a procedure called leukapheresis for a peripheral blood stem cell transplant (PBSC). In addition, novel research protocols are available for children who have either failed to respond to initial chemotherapy following diagnosis or who have relapsed after an initial response. These children are not candidates for the standard autologous transplant but may be eligible for combined targeted radiation therapy followed by an autologous transplant.

Severe combined immunodeficiency disease (SCID) represents a group of diseases with many different causes but, in general, results in children who have severe defects in the function of their lymphocytes. Currently, bone marrow stem cell transplantation is the only known treatment for children with SCID. Lymphocytes are a type of white blood cell in the body which are crucial for fighting infections. They consist of two general types of cells, T cells and B cells. T cells are responsible for fighting all types of germs, but they may also cause rejection of donor bone marrow and/or reactions called Graft Versus Host Disease (GVHD). GVHD occurs when T cells from the donor attack certain tissues (e.g., skin, liver, intestines) of the recipient. B cells are essential for making certain chemicals or proteins called antibodies that help protect against bacterial and viral infections. Antibodies can be purified from healthy, normal blood donors and administered to children with SCID in the form of gammaglobulin infusions or injections. Another type of white cell in the blood is called a natural killer (NK) cell. The exact function of NK cells is unknown, although it is thought that they may be important in rejecting donor bone marrow following the bone marrow transplant. Some patients with SCID have low to absent function of their NK cells.

Allogeneic stem cell transplantation is the only known treatment for a variety of genetic diseases called "inborn errors of metabolism" or "storage diseases." Each of these diseases is due to the deficiency of an enzyme, which results in the accumulation of toxic chemicals inside the cells. Depending upon the enzyme abnormality and the chemicals that accumulate, specific patterns of tissue damage and organ failure occur. These include central nervous system deterioration, growth failure, bone abnormalities and joint disability, enlargement of the liver and spleen in the abdomen, heart disease, airway obstruction, lung disease, corneal clouding and hearing loss. The eventual organ damage and outcome of the different diseases is quite variable, although the ones in which stem cell transplantation has been evaluated are those that have a naturally progressive downward course ultimately ending in death in childhood. The purpose of stem cell transplantation in these disorders is to provide special marrow-derived cells, which travel to various organs in the body including the liver (Kupffer cells), skin (Langerhan's cells), lung (alveolar macrophages), spleen (macrophages), lymph nodes, tonsils and the brain (microglia).

In the large majority of cases, the donors have been HLA matched siblings. In successfully engrafted patients, the abnormal facial and body features are ameliorated, the joint function is improved, and the cardiopulmonary and hepatic and splenic abnormalities disappear. The longer term effect on growth and skeletal maturation, and the effects on existing bone disease are not well defined. Of greatest significance is the effect on the central nervous system. While the damage to the brain, which has occurred up to the time of transplant, is not reversed, it does appear in long term studies that further psychomotor degeneration is either prevented or markedly reduced. For some of the genetic diseases, such as Hurler's, osteopetrosis and Fanconi's, it is known that a bone marrow transplant can be effective. For others, the benefit is not as clear and more studies are needed. Unfortunately, at least 80% of children with a storage disease who might benefit from a bone marrow transplant will not have an HLA matched sibling donor.
Review History
December 2005  Medical Advisory Council initial approval
December 2006  Medical Advisory Council no changes
January 2008  Update. No revisions.
March 2011  Update – no revisions
January 2012  Update. Added revised Medicare Table. No revisions.
January 2013  Update – No revisions
January 2014  Update – no revisions
January 2015  Update – no revisions
January 2016  Update – no revisions

This policy is based on the following evidence-based guidelines:
2. Children's Neuroblastoma Cancer Foundation.

References – Update January 2016

**References – Update January 2015**


**References – Update January 2014**


References – Update January 2013

References – Update January 2012

References – Update March 2011


References – Update January 2008


http://www.cancer.gov/cancertopics/pdq/treatment/ewings/healthprofessional

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References – Initial


**Important Notice**

**General Purpose.**
Health Net's National Medical Policies (the "Policies") are developed to assist Health Net in administering plan benefits and determining whether a particular procedure, drug, service or supply is medically necessary. The Policies are based upon a review of the available clinical information including clinical outcome studies in the peer-reviewed published medical literature, regulatory status of the drug or device, evidence-based guidelines of governmental bodies, and evidence-based guidelines and positions of select national health professional organizations. Coverage determinations are made on a case-by-case basis and are subject to all of the terms, conditions, limitations, and exclusions of the member's contract, including medical necessity requirements. Health Net may use the Policies to determine whether under the facts and circumstances of a particular case, the proposed procedure, drug, service or supply is medically necessary. The conclusion that a procedure, drug, service or supply is medically necessary does not constitute coverage. The member's contract defines which procedure, drug, service or supply is covered, excluded, limited, or subject to dollar caps. The policy provides for clearly written, reasonable and current criteria that have been approved by Health Net's National Medical Advisory Council (MAC). The clinical criteria and medical policies provide guidelines for determining the medical necessity criteria for specific procedures, equipment, and services. In order to be eligible, all services must be medically necessary and otherwise defined in the member's benefits contract as described this "Important Notice" disclaimer. In all cases, final benefit determinations are based on the applicable contract language. To the extent there are any conflicts between medical policy guidelines and applicable contract language, the contract language prevails. Medical policy is not intended to override the policy that defines the member's benefits, nor is it intended to dictate to providers how to practice medicine.

**Policy Effective Date and Defined Terms.**
The date of posting is not the effective date of the Policy. The Policy is effective as of the date determined by Health Net. All policies are subject to applicable legal and regulatory mandates and requirements for prior notification. If there is a discrepancy between the policy effective date and legal mandates and regulatory requirements, the requirements of law and regulation shall govern. * In some states, prior notice or posting on the website is required before a policy is deemed effective. For information regarding the effective dates of Policies, contact your provider representative. The Policies do not include definitions. All terms are defined by Health Net. For information regarding the definitions of terms used in the Policies, contact your provider representative.

**Policy Amendment without Notice.**

Stem Cell Transplants Pediatric Jan 16
Health Net reserves the right to amend the Policies without notice to providers or Members. In some states, prior notice or website posting is required before an amendment is deemed effective.

No Medical Advice.
The Policies do not constitute medical advice. Health Net does not provide or recommend treatment to members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

No Authorization or Guarantee of Coverage.
The Policies do not constitute authorization or guarantee of coverage of particular procedure, drug, service or supply. Members and providers should refer to the Member contract to determine if exclusions, limitations, and dollar caps apply to a particular procedure, drug, service or supply.

Policy Limitation: Member’s Contract Controls Coverage Determinations.
Statutory Notice to Members: The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illnesses or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. The determination of coverage for a particular procedure, drug, service or supply is not based upon the Policies, but rather is subject to the facts of the individual clinical case, terms and conditions of the member’s contract, and requirements of applicable laws and regulations. The contract language contains specific terms and conditions, including pre-existing conditions, limitations, exclusions, benefit maximums, eligibility, and other relevant terms and conditions of coverage. In the event the Member’s contract (also known as the benefit contract, coverage document, or evidence of coverage) conflicts with the Policies, the Member’s contract shall govern. The Policies do not replace or amend the Member’s contract.

Policy Limitation: Legal and Regulatory Mandates and Requirements
The determinations of coverage for a particular procedure, drug, service or supply is subject to applicable legal and regulatory mandates and requirements. If there is a discrepancy between the Policies and legal mandates and regulatory requirements, the requirements of law and regulation shall govern.

Reconstructive Surgery
CA Health and Safety Code 1367.63 requires health care service plans to cover reconstructive surgery. “Reconstructive surgery” means surgery performed to correct or repair abnormal structures of the body caused by congenital defects, developmental abnormalities, trauma, infection, tumors, or disease to do either of the following:

1. To improve function or
2. To create a normal appearance, to the extent possible.

Reconstructive surgery does not mean “cosmetic surgery,” which is surgery performed to alter or reshape normal structures of the body in order to improve appearance.

Requests for reconstructive surgery may be denied, if the proposed procedure offers only a minimal improvement in the appearance of the enrollee, in accordance with the standard of care as practiced by physicians specializing in reconstructive surgery.

Reconstructive Surgery after Mastectomy
California Health and Safety Code 1367.6 requires treatment for breast cancer to cover prosthetic devices or reconstructive surgery to restore and achieve symmetry for the patient incident to a mastectomy. Coverage for prosthetic devices and reconstructive surgery shall be subject to the co-payment, or deductible and coinsurance conditions, that are applicable to the mastectomy and all other terms and conditions applicable to other benefits. "Mastectomy" means the removal of all or part of the breast for medically necessary reasons, as determined by a licensed physician and surgeon.

Policy Limitations: Medicare and Medicaid
Policies specifically developed to assist Health Net in administering Medicare or Medicaid plan benefits and determining coverage for a particular procedure, drug, service or supply for Medicare or Medicaid members shall not be construed to apply to any other Health Net plans and members. The Policies shall not be interpreted to limit the benefits afforded Medicare and Medicaid members by law and regulation.