

MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	AUTOLOGOUS HEMATOPOIETIC (STEM) CELL TRANSPLANTATION
Policy Number	7.02.03
Category	Transplants
Effective Date	10/18/01
Revised Date	03/21/02, 06/19/03, 06/17/04, 05/18/05, 03/16/06, 05/17/07, 07/17/08, 10/29/09, 10/28/10, 12/15/11, 10/18/12, 10/17/13, 10/16/14, 10/15/15, 10/20/16, 11/16/17, 11/15/18
Product Disclaimer	<ul style="list-style-type: none"> If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply. If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit. If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.

POLICY STATEMENT

Based upon our criteria and review of the peer-reviewed literature, high-dose chemotherapy (HDC) with autologous hematopoietic (stem) cell support has been medically proven to be effective and therefore **medically appropriate** for carefully selected candidates. The following is a listing of coverage criteria for different medical conditions.

I. <u>Leukemias:</u>	
Medically appropriate indications: <u>Adult AML:</u> <ul style="list-style-type: none"> In the first remission but at high risk of relapse (<i>please refer to description section of this policy</i>) <u>Adult ALL:</u> <ul style="list-style-type: none"> In first remission at high risk of relapse (e.g., age greater than 35 years, and leukocytosis at presentation of greater than 30,000/μL (B-cell lineage), greater than 100,000/μL (T-cell lineage), or poor prognosis genetic abnormalities (e.g., presence of Philadelphia chromosome, extramedullary disease, and time to attain complete remission longer than 4 weeks) <u>Pediatric ALL:</u> <ul style="list-style-type: none"> In first complete remission but at high risk of relapse (e.g., age, WBC greater than or equal to 50,000/μL, hypodiploidy (less than 45 chromosomes) t(9:22) or <i>BCR/ABL</i> fusion t(4;11) or <i>MLL/AF4</i> fusion); or In second or greater remission or refractory ALL 	Investigational indications: <u>Adult ALL:</u> <ul style="list-style-type: none"> In second or greater remission or with refractory disease <u>Chronic lymphocytic leukemia (CLL)</u> <u>Small lymphocytic leukemia (SLL)</u> <u>Chronic myelogenous leukemia (CML)</u>
II. <u>Lymphomas</u>	
<u>Hodgkin Lymphomas:</u>	
Medically appropriate indications: <ul style="list-style-type: none"> Primary refractory or relapsing after completion of an initial or subsequent course of chemotherapy 	Investigational indications: <ul style="list-style-type: none"> Initial therapy for all HL to consolidate a first complete remission A second autologous hematopoietic (stem) cell transplant for relapsed lymphoma after a prior autologous transplant.

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<u>Non Hodgkin Lymphoma:</u>	
Non Hodgkin Lymphoma (NHL) can be classified as either indolent (low grade) or aggressive (intermediate or high grade)	
Medically appropriate indications:	Investigational indications:
<p><u>Aggressive</u></p> <ul style="list-style-type: none">• Salvage therapy when a complete response after full first-line induction chemotherapy is not achieved; or• To achieve or consolidate a complete or partial response in a chemosensitive first or second relapse; or• To consolidate a first complete or partial response in patients with Diffuse Large B-cell lymphoma at high or high-intermediate risk of relapse as predicted by the international prognostic index (IPI)**; or• Primary therapy for intermediate or aggressive subtypes with high International Prognostic Index** (IPI) score and for Burkitt-like Ki-67 positive Non-Hodgkin's Lymphoma.• Salvage therapy when a complete response after full first-line induction chemotherapy is not achieved for <i>low</i> or <i>high</i> risk Burkitt lymphoma <p><u>Indolent</u></p> <ul style="list-style-type: none">• Salvage therapy for patients who do not achieve a complete response after a full dose of first-line induction chemotherapy; or• To achieve or consolidate a complete or partial response for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has undergone transformation to a higher grade <p><u>Waldenstrom's macroglobinemia</u></p> <ul style="list-style-type: none">• As salvage therapy of chemosensitive Waldenstrom macroglobulinemia <p><u>Mantle Cell Lymphoma</u></p> <ul style="list-style-type: none">• To consolidate a first remission (complete or partial) <p><u>Peripheral T Cell Lymphoma (e.g., Mycosis fungoides/Sezary syndrome, primary cutaneous anaplastic large-cell lymphoma)</u></p> <ul style="list-style-type: none">• To consolidate a first remission in high risk Peripheral T-Cell Lymphoma• As salvage therapy <p><u>Primary CNS Lymphoma</u></p> <ul style="list-style-type: none">• To consolidate a first remission• As salvage therapy for relapsed or refractory primary CNS Lymphoma	<ul style="list-style-type: none">• Initial therapy for all other subgroups of NHL except intermediate or aggressive subtypes with high IPI score** as listed in the medically appropriated indications• To consolidate a first complete response for patients with Diffuse Large B-cell lymphoma with a low or low-intermediate risk of relapse as predicted by the IPI**• To consolidate a first complete response for those with indolent lymphoma subtypes• Tandem transplants• As salvage therapy for Mantle Cell lymphoma

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<p>Examples of lymphomas as described by the World Health Organization (WHO) and the Revised European-American Classification of Lymphoid Neoplasms (REAL). This list is not all-inclusive. (* denotes indolent types of lymphoma while + denotes aggressive type)</p>	
<p>B-cell Neoplasms Precursor B-cell Neoplasms</p> <ul style="list-style-type: none"> • Precursor B-lymphoblastic leukemia/lymphoma⁺ <p>Mature (Peripheral) B-cell Neoplasms-Predominately Disseminated</p> <ul style="list-style-type: none"> • CLL/SLL* • B-Prolymphocyte lymphoma⁺ • Lymphoplasmacytic lymphoma* (includes Waldenstrom’s Macroglobulinemia) • Splenic Marginal Zone lymphoma* • Hairy cell lymphoma* • Plasma cell myeloma/plasmacytoma <p>Mature (Peripheral) B-cell Neoplasms-Primary Extranodal Mucosa-associated lymphoid tissue*</p> <p>Mature (Peripheral) B-cell Neoplasms-Predominantly Nodal</p> <ul style="list-style-type: none"> • Marginal Zone lymphoma* • Follicular lymphoma* • Mantle cell lymphoma⁺ • Intravascular LBCL⁺ • Primary effusion lymphoma⁺ • Burkitt’s lymphoma⁺ • Lymphomatoid granulomatosis 	<p>T- and NK-cell Neoplasms Precursor T- and NK-cell Neoplasms</p> <ul style="list-style-type: none"> • Precursor T-lymphoblastic leukemia/lymphoma⁺ • Blastoid NK lymphoma⁺ <p>Mature (Peripheral) T-cell Neoplasms-Predominately Disseminated</p> <ul style="list-style-type: none"> • T-cell Prolymphocytic leukemia⁺ • T-cell Large Granular Lymphocytic leukemia* • Aggressive NK-cell leukemia⁺ Adult T-cell lymphoma/leukemia-HTLV-1⁺ <p>Mature (Peripheral) T-cell Neoplasms- Primary Extranodal</p> <ul style="list-style-type: none"> • Extranodal NK/T-cell lymphoma, nasal type⁺ • Enteropathy-type T-cell lymphoma⁺ • Hepatosplenic T-cell lymphoma⁺ • Subcutaneous panniculitis-like T-cell lymphoma⁺ • Mycosis fungoides/Sezary syndrome* • Primary cutaneous anaplastic large-cell lymphoma⁺ <p>Mature (Peripheral) T-cell Neoplasms-Predominantly Nodal</p> <ul style="list-style-type: none"> • Peripheral T-cell lymphoma- NOS⁺ • Angioimmunoblastic T-cell lymphoma⁺ <p>Primary systemic anaplastic Large-cell lymphoma⁺</p>
<p>**International Prognostic Index: Low Risk = 0-1 points, Low Intermediate = 2, High Intermediate = 3, High Risk = 4-5 points</p>	
<p><u>0 points</u></p> <ul style="list-style-type: none"> • Age less than 60 years • Tumor stage I or II • Extranodal Involvement (ENI) 0-1 • Performance status (PS) Eastern Cooperative Oncology Group (ECOG) 0-1 • Lactate dehydrogenase (LDH) normal 	<p><u>1 point for presence of each</u></p> <ul style="list-style-type: none"> • Age greater than 60 years • Tumor stage III or IV • ENI greater than 1 • PS (ECOG) 2-4 • LDH greater than normal
<p>**International Follicular Lymphoma Prognostic Index: Low Risk = 0-1 points, Intermediate Risk = 2, High Risk= greater than 5 points</p>	
	<p><u>1 point for presence of each</u></p> <ul style="list-style-type: none"> • Age greater than or equal to 60 years • Ann Arbor stage III-IV • Hemoglobin level less than 12 g/dL • Serum LDH level greater than the upper limit of normal • Number of nodal sites greater than or equal to 5

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<u>III. Solid Tumors of Childhood</u>		
Defined as not arising from myeloid or lymphoid cells. The most common are neuroblastoma, Ewing’s sarcoma, Wilms’ tumor, rhabdomyosarcoma, osteosarcoma, or retinoblastoma. Neuroblastoma is classified into low, intermediate and high risk based on the stage and the number of copies of the N-myc oncogene		
<u>Low Risk</u> Stage I Stage II; N-myc = 1 Stage IVS	<u>Intermediate Risk</u> Stage III and N-myc = 1 and ferritin less than 143 and favorable histology Stage IV and N-myc =1 and less than 1 year at diagnosis Stage III and less than 1 year at diagnosis	<u>High Risk</u> Stage II and greater than 10 N-myc Stage III; greater than 10 N-myc or ferritin greater than 143 or unfavorable histology Stage IV and greater than 1 year at diagnosis Stage IV at greater than 1 year at diagnosis and greater than 10 N-myc
Medically appropriate indications:		Investigational indications:
<ul style="list-style-type: none"> • Initial treatment of high risk neuroblastoma; or • Primary refractory or recurrent neuroblastoma; or • Initial treatment of high risk Ewing’s sarcoma; or • Recurrent or refractory Ewing’s sarcoma; or • Tandem transplantation for high-risk neuroblastoma; or • Metastatic retinoblastoma 		<ul style="list-style-type: none"> • Initial treatment of low or intermediate risk Ewing’s sarcoma and neuroblastoma; or • Treatment of Wilms’ tumor, rhabdomyosarcoma, osteosarcoma, retinoblastoma without metastasis; or • Tandem or multiple transplants for treatment of pediatric solid tumors (except high risk neuroblastoma)
<u>IV. Germ Cell Tumors</u>		
Comprise the vast majority of primary testicular neoplasms, although can also arise in the ovary and in extragonadal locations.		
Medically appropriate indications:		Investigational indications:
<ul style="list-style-type: none"> • Germ cell tumors that do not achieve complete remission, (e.g., refractory germ cell tumors or those exhibiting a partial response) ; or • Unfavorable prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease; or • Tandem or sequential autologous HCT either as salvage therapy or with platinum-refractory disease 		<ul style="list-style-type: none"> • Initial treatment (e.g., in lieu of an initial course of conventional 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)
<u>V. Multiple Myeloma</u>		
Medically appropriate indications:		Investigational indications:
<ul style="list-style-type: none"> • Single or tandem transplant for newly diagnosed or responsive multiple myeloma; or • Second autologous HCT to treat responsive myeloma that has relapsed after a durable complete or partial remission following an initial autologous transplant; or • Tandem transplantation with an initial round of autologous hematopoietic (stem) cell transplantation (HCT) followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic (stem) cell transplantation to treat newly diagnosed multiple myeloma patients 		

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VI. <u>Amyloidosis</u>	
Medically appropriate conditions:	Investigational indications:
<ul style="list-style-type: none"> • Amyloidosis with involvement of fewer than 2 organ systems • Amyloid cardiac involvement is NOT an absolute contraindication to proceeding to BMT. Interventricular septal thickness and ejection fraction should be measured with all patients. 	<ul style="list-style-type: none"> • Amyloidosis with involvement of greater than 2 organ systems
VII. <u>Primitive Neuroectodermal Tumor (PNET)</u>	
<p>PNET include neuroblastoma arising in the central nervous system, ependyoblastoma, or pinealblastoma. All show a similar histology and are principally distinguished by their site of origin.</p>	
Medically appropriate conditions:	Investigational indications:
<ul style="list-style-type: none"> • Recurrent medulloblastoma and other primitive neuroectodermal tumors (PNETs) or • As consolidation therapy for previously untreated embryonal tumors (PNET) of the central nervous system that show partial or complete response to induction chemotherapy, or stable disease after induction therapy; or • Recurrent embryonal tumors 	<ul style="list-style-type: none"> • Treatment of ependymoma. • Tandem transplant for patients with medulloblastoma, other PNETs of the CNS, or ependymoma
VIII. <u>Other Malignant Conditions</u>	
<p>Based upon our criteria and review of the peer-reviewed literature, treatment with HDC and autologous hematopoietic (stem) cell transplant for the following malignant conditions has not been medically proven to be effective and therefore is considered investigational:</p>	
<ul style="list-style-type: none"> • Breast cancer • Epithelial ovarian cancer • Lung cancer, any histology • Pancreas cancer • Esophageal cancer • Cancer of the bile duct • Cervical cancer • Cancer of the fallopian tubes • Nasopharyngeal cancer • Neuroendocrine tumors • Thyroid tumors • Malignant astrocytomas and gliomas including glioblastoma multiforme & oligodendroglioma 	<ul style="list-style-type: none"> • Colon cancer • Rectal cancer • Stomach cancer • Gall bladder cancer • Renal cell cancer • Uterine cancer • Prostate cancer • Paranasal sinus cancer • Soft tissue sarcomas • Tumors of the thymus • Tumors of unknown primary origin • Malignant Melanoma
IX. <u>Non-malignant Diseases</u>	
<u>Autoimmune Diseases</u>	
<p>Based upon our criteria and review of the peer-reviewed literature, treatment with HDC and autologous bone marrow/(stem) hematopoietic cell transplant for autoimmune conditions has not been medically proven to be effective and therefore is considered investigational for all Autoimmune Diseases, including but not limited to:</p>	
<ul style="list-style-type: none"> • Rheumatoid and juvenile idiopathic arthritis • Systemic sclerosis (e.g., scleroderma) • Systemic lupus erythematosus (SLE) 	<ul style="list-style-type: none"> • Multiple sclerosis • Type 1 diabetes mellitus • Chronic inflammatory demyelinating polyneuropathy

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POLICY GUIDELINES

Pre-Transplant Evaluation Guidelines:

- I. Clinical Evaluation:
 - A. Confirmation of diagnosis;
 - B. Identification of comorbidities;
 - C. Treatment of co-morbidities;
 - D. Current assessment of co-morbidities;
 - E. Consult notes (if applicable).
- II. Psycho-Social Evaluation:
 - A. Karnofsky performance score;
 - B. Identification of stressors (family support, noncompliance issues, motivational issues, alcohol or substance abuse).
- III. Dental Evaluation.
- IV. Lab Tests:
 - A. CBC, metabolic profile;
 - B. Serologies: CMV, Hepatitis B and C;
 - C. HIV testing.
- V. Cardiac Assessment:
 - A. 12 lead EKG;
 - B. Stress echo or MUGA scan.
- VI. Pulmonary Assessment:
 - A. Chest x-ray;
 - B. Pulmonary function tests (PFTs).
- VII. Age Appropriate Screening Tests:
 - A. Age greater than or equal to 50 years: Guaiac stool testing (within 1 year).
 - B. Women Age 21-70 years: Pap Smear (within 3 years).
 - C. Women Age greater than or equal to 40 years: Mammogram (within 2 years)

Recipient Selection Guidelines:

Each individual considered for autologous stem cell transplant will be evaluated by the transplant center for potential difficulties that would complicate and diminish the success of transplantation. Consideration will be given to the patient's risk of death without transplantation, along with the presence and severity of potential contraindications to transplantation.

DESCRIPTION

Stem cells differ from other blood cells in that they are capable of both unlimited self-renewal and differentiation to form white blood cells, red blood cells or platelets. Stem cells can be collected from two sources: direct aspiration of bone marrow *or* through a pheresis procedure to harvest peripheral blood stem cells (PBSC). Prior to harvesting the stem cells, pretreatment with drugs called "growth factors" or "colony stimulating factors" may be given to enhance stem cell production. The harvested stem cells are then cryopreserved until transplanted.

In autologous (stem) cell transplantation (AuSCT) a portion of the patient's own stem cells are re-infused intravenously to rescue the patient by re-establishing his/her bone marrow which has been eradicated after high dose chemotherapy (HDC) and/or total body irradiation has been given to destroy the malignant cells. Tandem transplantation is defined as two planned courses of high-dose chemotherapy with stem cell support.

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Classification of the risk of disease for acute myeloid leukemia has been identified in the National Comprehensive Cancer Network treatment guidelines (2013). Risk is based on cytogenetic stratification of good, intermediate and poor-risk AML. Treatment depends on which risk category of the disease.

Risk Status	Cytogenetics	Molecular Abnormalities
Favorable-risk	Core binding factor: <ul style="list-style-type: none">• inv(16)• t(8;21)• t(16;16)• t(15;17)	<ul style="list-style-type: none">• Normal cytogenetics:• NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate risk	<ul style="list-style-type: none">• Normal cytogenetics• +8• t(9;11)• Other non-defined	
Poor-risk	<ul style="list-style-type: none">• Complex (greater than or equal to 3 clonal chromosomal abnormalities)• Monosomal karyotype• -5• -7• 5q-• 7q-• 11q23 – non t(9;11),• Inv(3)• t(3;3)• t(6;9)• t(9;22)	<ul style="list-style-type: none">• Normal cytogenetics with FLT3 ITD mutation**• TP53 mutation

**FLT3-ITD mutations are considered to confer a significantly poorer outcome in patients with normal karyotype, and these patients should be considered for clinical trials where available. There is controversy as to whether FLT3-TKD mutations carry an equally poor prognosis.

Non-Hodgkin Lymphomas (NHLs) are often divided into two groups, indolent and aggressive depending on the types of affected cells and the rate of growth of the cells. Indolent Non-Hodgkin Lymphomas (NHLs) tend to grow and spread slowly with few symptoms. They are low-grade cancers which are often very responsive to treatments like chemotherapy, radiation, and immunotherapy. However treatment is often deferred until the patient becomes symptomatic. The goal of treatment is often management as indolent lymphomas are rarely cured, unless it is diagnosed when still localized. Thus, treatment options are more varied with no standardization. Aggressive Non-Hodgkin Lymphomas (NHLs) are fast growing and are described as intermediate or high grade. They can be treated with chemotherapy, radiotherapy, monoclonal antibody therapy or a combination. The decision on the exact course of treatment is usually decided on a number of factors such as, the stage of the disease, the number of nodes involved, the presence of lymphoma in other organs, and age.

RATIONALE

Published studies demonstrate that autologous (stem) hematopoietic cell and bone marrow transplantation improve health outcomes for patients with certain diagnoses who meet specific criteria. Improved outcomes have been achieved outside the investigational setting for those patients. Available evidence does not demonstrate improved outcomes in other diagnoses and/or where listed criteria are not met.

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- Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.
- **CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.**
- Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

CPT Codes

Code	Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38210	specific cell depletion within harvest, T-cell depletion
38211	tumor cell depletion
38212	red blood cell removal
38213	platelet depletion
38232	Bone marrow harvesting for transplantation, autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

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Code	Description
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

ICD10 Codes

Code	Description
C26.0-C26.9	Malignant neoplasm of other and ill-defined digestive organs (code range)
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung (code range)
C38.1-C38.8	Malignant neoplasm of mediastinum and pleura (code range)
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system (code range)
C48.0	Malignant neoplasm of retroperitoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue (code range)
C50.011- C50.919	Malignant neoplasm of breast (code range)
C62.00-C62.92	Malignant neoplasm of testis (code range)
C71.0-C71.9	Malignant neoplasm of brain (code range)
C81.00-C81.99	Hodgkin lymphoma (code range)
C82.00-C82.99	Follicular lymphoma (code range)
C83.00-C83.09	Non-follicular lymphoma (code range)
C83.10-C83.19	Mantle cell lymphoma (code range)

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Code	Description
C83.30-C83.39	Diffuse large B-cell lymphoma (code range)
C83.50-C83.59	Lymphoblastic (diffuse) lymphoma (code range)
C83.70-C83.79	Burkitt lymphoma (code range)
C83.80-C83.99	Other non-follicular lymphoma (code range)
C84.60-C84.79	Anaplastic large cell lymphoma, ALK-positive (code range)
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferations
C88.2-C88.9	Malignant immunoproliferative diseases and certain other B-cell lymphomas (code range)
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms (code range)
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type (code range)
E85.0-E85.9	Amyloidosis (code range)
G35	Multiple sclerosis
M05.00-M05.09	Felty's syndrome (code range)
M05.20-M05.29	Rheumatoid vasculitis with rheumatoid arthritis (code range)
M05.30-M05.39	Rheumatoid heart disease with rheumatoid arthritis (code range)
M05.40-M05.59	Rheumatoid myopathy with rheumatoid arthritis (code range)
M05.60-M06.09	Rheumatoid arthritis with involvement of other organs and systems (code range)
M06.1	Adult-onset Still's disease
M06.4	Inflammatory polyarthropathy
M06.80-M06.9	Other specified rheumatoid arthritis (code range)
M08.00-M08.99	Juvenile arthritis (code range)
M12.00-M12.09	Other and unspecified arthropathy (code range)
M32.0-M32.9	Systemic lupus erythematosus (SLE) (code range)
M34.0-M34.9	Systemic sclerosis [scleroderma] (code range)

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*Key Article

KEY WORDS

Autologous bone marrow transplant, Autologous stem cell transplant

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD) for Stem Cell Transplantation. Please refer to the following NCD website for Medicare Members: <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&bc=AgAAgAAAAAAAAAA%3d%3d&>