NO. 91066

STEM CELL OR BONE MARROW TRANSPLANTATION

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Policy scope: This policy defines the medical necessity criteria for allogeneic and autologous stem cell, bone marrow, and other hematopoietic cell transplants, specifying the clinical conditions and patient eligibility requirements under which these procedures are considered medically necessary.

Related policies:

- Experimental/Investigational/Unproven Care/Benefit Exceptions medical policy # 91117
- Clinical Trials for Self-Funded Groups Opting Out of PPACA # 91448
- Clinical Trials # 91606

I. MEDICAL NECESSITY CRITERIA

General Coverage Criteria for all Stem Cell or Bone Marrow or other Blood Cell Transplants

A. Allogeneic or Autologous Bone Marrow, Peripheral Stem Cell, or other Blood Cell Transplants are a covered benefit for specific indications that are not experimental or investigational and for which the procedure has been proven to be effective.

General guidelines for consideration for bone marrow/stem cell transplantation must be met. These guidelines include, but are not limited to, the following:

1. The member must meet all of the criteria below:
    a. Adequate major organ function and lack of major systemic complications to include adequate liver function, cardiac function, pulmonary function, and renal function.
    b. Predicted ability to tolerate the surgical procedure as well as the post-transplant immunosuppression regimen and potential complications.
    c. Emotional and psychiatric stability, including a strong family or alternative support network (documented by formal social work evaluation).
    d. Ability to understand the risks of the procedures

2. Priority Health does not cover bone marrow/stem cell transplantation when any of the following conditions are present:

    a. Presence of psychiatric disease that would interfere with the member's ability to comply with the pre-or post-transplant therapeutic regimen.

    b. Significant history of medical noncompliance.
    c. Unwillingness or inability to adhere to post transplant lifestyle restrictions and medical regimen.

B. Transportation and lodging for the patient, donor or family are not covered benefits, unless otherwise specified in coverage documents.

C. Experimental, investigational, or unproven bone marrow, peripheral stem cell, or other blood cell transplants are not a covered benefit unless coverage is determined to be appropriate under the Experimental/Investigational/Unproven Care/Benefit Exceptions medical policy (# 91117), the Clinical Trials for Self-Funded Groups Opting Out of PPACA (# 91448) or the Clinical Trials (# 91606) medical policy.

D. All Bone marrow, Peripheral Stem Cell, or other Blood Cell Transplants must be pre-authorized by Priority Health and performed at a Priority Health approved facility. Requests for authorization should be submitted on the Bone Marrow/Peripheral Stem Cell or Other Blood Cell Transplant prior authorization form.

E. Transplant referrals are directed to facilities in Priority Health's network or contracted networks. For more information, please refer to the Provider Manual.

F. An approved Bone Marrow, Peripheral Stem Cell, or other Blood Cell Transplant includes coverage for the following:
    1. Pre-transplant care, including the transplant evaluation. One evaluation per transplant. Note: A second opinion consult only to determine transplant candidacy would be approved at a contracted or in network transplant facility if a second transplant evaluation is requested and the member has been previously turned down for transplant.
    2. Transplant care, facility, and professional fees.

3. Harvesting of donor. Priority Health will cover donor fees for transplant recipients who are members, unless donor fees are covered by another Health Plan.
4. Post-Transplant immunosuppressant drug therapy if the group has outpatient prescription drug coverage.
5. Post-transplant care:
    a. Follow-up care and services are covered at the transplant facility for one year following the transplant, for both contracted and non-contracted transplant facilities.
    b. Follow-up care beyond one year post-transplant:
        i. Covered at contracted transplant facilities.
        ii. Non-contracted facilities: only physician services are covered. Testing, labs, and imaging are covered in network only.

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Stem Cell Transplant for Treatment of Non-Malignant Conditions

Allogeneic bone marrow transplants may be considered medically necessary for selected patients with the following disorders:

- Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage, and with an HLA-identical donor. Factors associated with a high risk of stroke or end-organ damage include: recurrent chest pain syndrome, recurrent vaso-occlusive crises, red blood cell alloimmunization or chronic transfusion therapy
- Severe or very severe aplastic anemia, including congenital (e.g., Fanconi's anemia or Diamond-Blackfan syndrome) or acquired (e.g., secondary to drug or toxin exposure) forms. Appropriate patients include those with platelets less than 20 x 109 /L, granulocytes less than 0.5 x 109 /L, and reticulocytes less than 1% (corrected for hematocrit) and who have failed antithymocyte globulin therapy
- Homozygous beta-thalassemia (i.e., thalassemia major)
- Wiskott-Aldrich syndrome
- Severe combined immunodeficiencies
- Chediak-Higashi syndrome
- Infantile malignant osteopetrosis (Albers-Schönberg disease or marble bone disease)
- Mucopolysaccharidoses (e.g., Hunter's, Hurler's Sanfilippo, Maroteaux-Lamy variants) in patients who are neurologically intact)
- Mucolipidoses (e.g., Gaucher's disease, metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy) for patients who have failed conventional therapy (e.g., diet, enzyme replacement) and who are neurologically intact.
- Kostmann's syndrome (severe congenital neutropenia)
- Leukocyte adhesion deficiencies
- X-linked lymphoproliferative syndrome

Stem Cell Transplant for Autoimmune Diseases

Autologous hematopoietic stem cell transplantation for the treatment of multiple sclerosis may be considered medically necessary when all of the following criteria are met:

- Relapsing-remitting multiple sclerosis
- Breakthrough disease activity despite ongoing treatment with high-efficacy disease-modifying therapy, as evidenced by either of the following:
    - Two or more clinical relapses at separate times but within the previous 12 months
    - One relapse and a magnetic resonance imaging (MRI) gadolinium-enhancing lesion(s) at a separate time than the relapse but within the previous 12 months
- Expanded disability status scale [EDSS] score of 2.0 to 6.0
- Age <45
- Disease duration <10 years

Stem-cell transplantation (autologous or allogeneic) for the treatment of other autoimmunediseases, including, but not limited to any of the following indications, is considered experimental, investigational or unproven and not a covered benefit:

- autoimmune hemolytic anemia

- autoimmune hepatitis
- celiac disease
- Crohn's disease
- cryptogenic cirrhosis
- dermatomyositis
- immune vasculitis
- juvenile idiopathic arthritis
- neuromyelitis optica
- polymyositis
- rheumatoid arthritis
- systemic lupus erythematosus
- systemic sclerosis, also known as scleroderma
- thrombotic thrombocytopenia purpura
- type I diabetes mellitus
- ulcerative colitis

Stem Cell Transplant for Solid Tumors in Adults

Autologous or allogeneic hematopoietic stem cell transplant (ablative and non-myeloablative) for the treatment of any of the following solid tumors in adults is considered experimental and investigational because its effectiveness for these indications has not been established:

- bile duct
- breast
- central nervous system tumors (e.g., astrocytoma, choroid plexus tumors, ependymoma, gliomas, oligodendroglioma)
- cervix
- colon
- epithelial ovarian
- esophagus
- gallbladder
- kidney
- lung
- melanoma
- nasopharynx
- pancreas
- paranasal sinus
- prostate
- rectum
- renal cell carcinoma
- soft tissue sarcomas
- stomach
- thymus
- thyroid
- uterus

Stem Cell Transplant for Childhood Solid Tumors

High-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation is a covered benefit for the following:

- relapsed Wilms' tumor
- metastatic non-central nervous system (non-CNS) retinoblastoma
- relapsed or progressive Ewing family of tumors

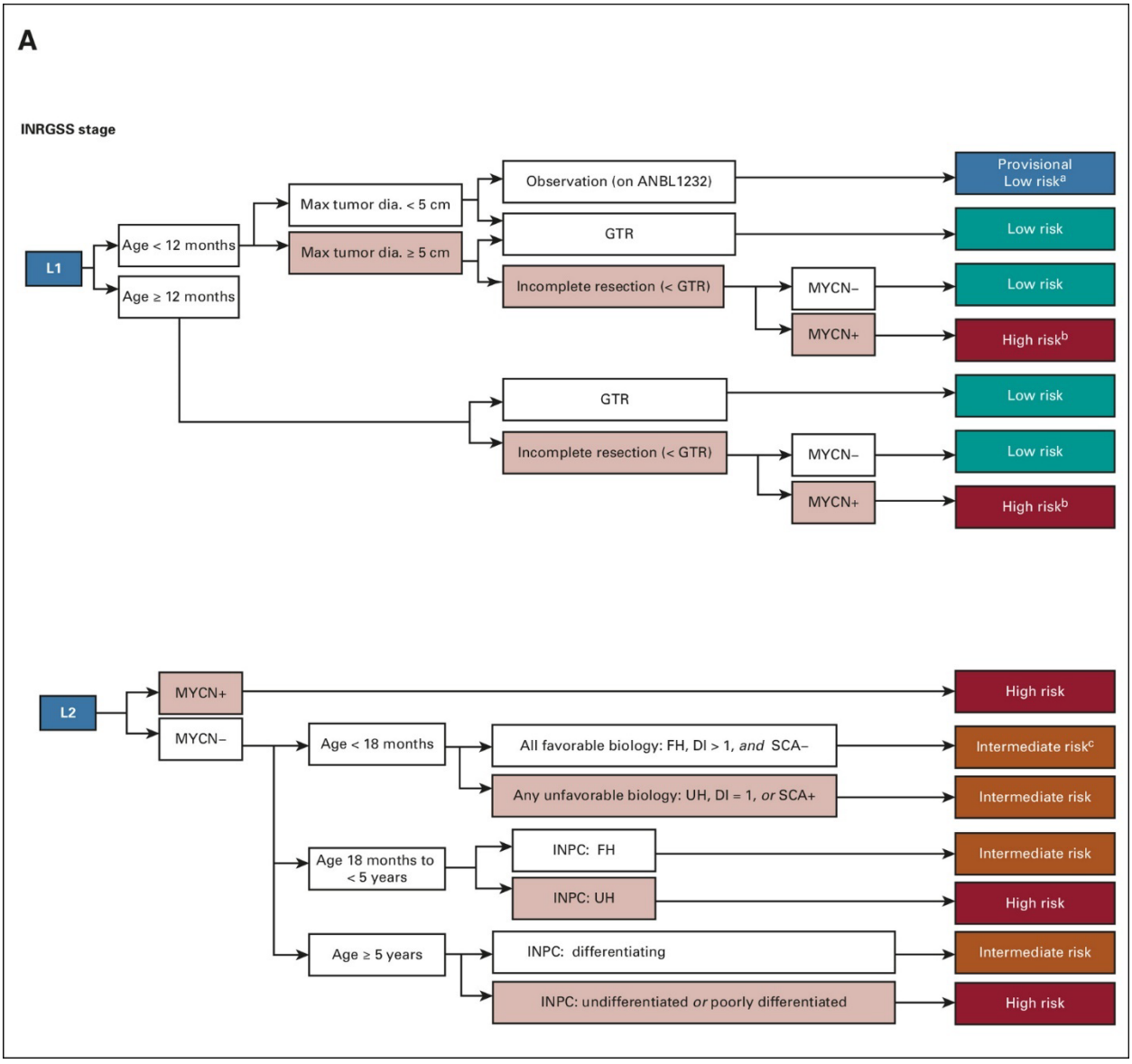
Stem Cell Transplant for Neuroblastoma

Autologous stem-cell transplantation (SCT) is a covered benefit for the treatment of high-risk neuroblastoma. A maximum of three tandem autologous HSCTs are covered for high-risk neuroblastoma.

Allogeneic SCT from an appropriately-matched human leukocyte antigen (HLA) donor following high-dose chemotherapy is covered for the treatment of high-risk neuroblastoma when the individual is not a candidate for autologous HSCT.

High Risk Neuroblastoma Definition:

Children's Oncology Group Neuroblastoma Risk Classifier (version 2)



Stem Cell Transplant for Primitive Neuroectodermal Tumors (PNET) and Ependymoma

Autologous stem cell transplantation is a covered benefit for the treatment of primitive neuroectodermal tumors (PNET) including medulloblastoma and pineoblastoma.

Allogeneic stem cell transplantion is considered experimental and investigational for the treatment of PNET including medulloblastoma and pineoblastoma because of insufficient evidence of its safety and effectiveness.

Autologous stem cell transplantation is a covered benefit for the treatment of ependymoma if patient is ineligible for radiotherapy.

Allogeneic stem cell transplantation is considered experimental and investigational for the treatment of ependymoma because of insufficient evidence of its safety and effectiveness.

Stem Cell Transplant for Treatment of Ovarian or Testicular Germ Cell Tumors

Single or tandem autologous hematopoietic stem-cell transplantation (SCT) is a covered benefit for relapsed or refractory testicular and ovarian germ cell tumors.

The following procedures are experimental, investigational or unproven and not covered for germ cell cancers:

- autologous SCT as front-line therapy
- allogeneic SCT

Note: SCT is not covered for epithelial ovarian cancer (see section on solid tumors in adults)

Stem Cell Transplant for Hodgkin's Disease

High dose chemotherapy with either autologous or allogeneic stem cell support may be covered in patients with refractory, primary progressive or recurrent Hodgkin's disease.

Nonmyeloablative allogeneic SCT is covered for relapsed or refractory Hodgkin disease following a prior SCT. Nonmyeloablative allogeneic HSCT for any other indication is considered experimental and investigational.

Tandem stem cell transplant (sequential) for Hodgkin's disease is considered investigational.

Note: Relapse is the re-appearance of disease in regions of prior disease (recurrence) and/or in new regions (extension) after initial therapy and attainment of complete response.

Stem Cell Transplant for Non-Hodgkin's Lymphomas

Autologous or allogeneic stem cell is a covered benefit for relapsed or primary refractory non-Hodgkin's lymphoma (NHL).

High dose chemotherapy with autologous or allogeneic stem cell support is considered investigational as initial therapy of all non-Hodgkin's lymphomas.

Non-myeloablative allogeneic hematopoietic cell transplantation ("mini-transplant", reduced intensity conditioning transplant) may be covered for relapsed or primary refractory NHL when a reduced intensity regimen is preferred by the transplant center.

Tandem autologous hematopoietic cell transplantation (auto-auto) or tandem autologous stem cell transplantation followed by allogenic stem cell transplantation (auto-allo) is considered experimental and investigational for NHL.

Stem Cell Transplantation for Myelofibrosis

Allogeneic (ablative and non-myeloablative) stem cell transplantation is a covered benefit myelofibrosis (MF) when any of the following criteria is met:

- The individual is transfusion (RBC or Platelet) dependent; or
- The individual is resistant to conservative therapy; or
- The individual has intermediate or high risk MF

Repeat allogeneic (ablative or non-myeloablative) hematopoietic cell transplantation medically necessary for individuals with myelofibrosis and primary graft failure or who have relapsed. Autologous stem cell transplantation is considered experimental and investigational for myelofibrosis.

Stem Cell Transplant for Myelodysplastic Syndrome

Allogeneic (ablative and non-myeloablative) stem cell transplantation is a covered benefit for intermediate-risk or high-risk myelodysplastic syndrome (MDS) when individual has not responded to prior therapy and has an available human leukocyte antigen (HLA)-matched donor.

A repeat allogeneic (ablative or non-myeloablative) stem cell transplant is a covered benefit for individuals with intermediate-risk or high-risk MDS due to primary graft failure or failure to engraft.

A repeat allogeneic (ablative or non-myeloablative) SCT is considered experimental for individuals with MDS who have relapsed.

Autologous stem cell transplantation is considered experimental and investigational for MDS because the effectiveness has not been established.

Stem Cell Transplant for the Treatment of Chronic Myelogenous Leukemia (CML)

High dose chemotherapy with allogeneic stem cell support is a covered benefit for the treatment of chronic myelogenous leukemia.

High dose chemotherapy with autologous stem cell support is considered investigational as a treatment of chronic myelogenous leukemia.

Stem Cell Transplant for Acute Myelogenous Leukemia (AML)

Autologous or allogeneic stem cell transplant is a covered benefit for the treatment of AML in first complete remission, for primary refractory AML (i.e., leukemia that does not achieve a complete remission after conventional dose chemotherapy), or relapsed AML. Both ablative and non-myeloablative transplants are covered for these indications.

A repeat autologous or allogeneic hematopoietic cell transplantation (ablative or mini-allograft) is a covered benefit when the first autologous or allogeneic hematopoietic cell transplantation was unsuccessful due to primary graft failure or failure to engraft or for persons who have relapsed after a prior stem cell transplantation.

A repeat autologous or allogeneic stem cell transplantation (ablative or mini-allograft) for persistent or progressive disease is considered experimental and investigational.

Tandem stem cell transplant for AML is considered investigational and not a covered benefit.

Stem Cell Transplant as a Treatment of Acute Lymphocytic Leukemia (ALL)

Allogeneic stem cell transplantation is a covered benefit for the treatment of ALL, including primary refractory ALL (i.e., leukemia that does not achieve a complete remission after conventional dose chemotherapy), except for refractory relapse, defined as persons in relapse who are unresponsive to 3 or more months of adequate chemotherapy.

A non-myeloablative allogeneic hematopoietic cell transplantation, also known as mini-allograft or reduced intensity conditioning transplant, is a covered benefit for the treatment of ALL for members with no persistent disease who meet all of the selection criteria above. Note: Persons with persistent disease should not be candidates for a mini-allograft transplant.

A second myeloablative allogeneic HSCT from an appropriately-matched HLA donor is a covered benefit for the treatment of ALL when relapsed disease occurs more than six months after first allogeneic SCT.

Autologous stem cell transplantation is a covered benefit for ALL where no suitable donor is available.

Tandem stem cell transplant for ALL is considered experimental and not a covered benefit.

Stem Cell Transplant for Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

Allogeneic stem-cell transplantation is a covered benefit for the treatment of chronic lymphocytic leukemia (CLL) that is not responsive to standard therapy.

Autologous SCT is a covered benefit for the treatment of CLL in an individual in complete or good partial remission.

Stem Cell Transplant for Multiple Myeloma, Amyloidosis or Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and skin changes (POEMS syndrome)

1. **Multiple Myeloma**

   Autologous stem-cell transplantation is covered for the treatment of active (i.e., symptomatic) multiple myeloma (MM) for EITHER of the following indications:

   - after response to primary therapy
   - refractory to primary therapy in an individual with relapse or progressive disease

   A second course of autologous hematopoietic cell transplantation may be considered medically necessary for the treatment of responsive MM that has relapsed after a durable complete or partial remission following an autologous transplantation.

   A third autologous SCT for the treatment of active (i.e., symptomatic) MM is a covered benefit in an individual with progressive disease following a previous autologous HSCT.

Tandem (eg. Sequential or double) autologous transplants or autologous transplant followed by allogeneic transplant from an haploidentical to fully matched related donor or well-matched unrelated donor (i.e., meeting National Donor Marrow Program (NDMP) criteria for selection of unrelated donors) are considered medically necessary if planned 1st and 2nd transplantation are within a 6-month period and the member is considered high risk for progression/relapse.

Allogeneic SCT is a covered benefit from an appropriately-matched human leukocyte antigen (HLA) donor for the treatment of active (i.e., symptomatic) MM in an individual with progressive disease following autologous HSCT.

2. **Amyloidosis**

Autologous stem cell support is a covered benefit for primary systemic amyloidosis (e.g. Amyloid light chain, AL).

The following are considered experimental and investigational and are not covered for amyloidosis:

- second autologous SCT for the treatment of recurrent or refractory amyloidosis
- tandem autologous SCT
- allogeneic SCT

3. **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy and skin changes (POEMS Syndrome)**

Autologous SCT is a covered benefit.

Nonmyeloablative Allogeneic Stem Cell Transplantation for Treatment of Malignancy
Nonmyeloablative allogeneic stem cell transplantation ("mini-transplant," reduced intensity conditioning transplant) may be considered medically necessary in patients who would otherwise meet patient selection criteria for high dose chemotherapy and allogeneic stem cell transplantation for the following conditions.

- Non-Hodgkin lymphoma
- Hodgkin’s disease
- myelodysplastic diseases / myelodysplastic syndrome
- acute myelogenous leukemia
- chronic myelogenous leukemia
- acute lymphocytic/lymphoblastic leukemia
- chronic lymphocytic leukemia
- multiple myeloma
- aplastic anemia
- myelofibrosis
- neuroblastoma
- sickle cell anemia
- thalassemia major

Other applications of nonmyeloablative allogeneic stem cell transplantation are considered investigational, including its use in patients who do not meet criteria for high dose chemotherapy and allogeneic stem cell transplantation due to either age or co-morbidities, or as a treatment of other malignancies, including melanoma, or other solid tumors (e.g. renal cell carcinoma, breast cancer, ovarian cancer, testicular cancer).

Tandem Stem Cell Transplants

Tandem stem cell transplants may be a covered benefit for specific conditions if noted as covered in the applicable section of this policy. Use of tandem transplants for some conditions is considered experimental and investigational.

Umbilical Cord Blood Stem Cell Transplant (UCBSCT)

Priority Health covers UCBSCT in patients who meet all eligibility requirements for an allogeneic stem cell transplant. Priority Health does not cover UCBSCT for patients not meeting patient selection criteria for allogeneic stem cell transplant. This coverage decision is based on lack of evidence regarding safety and efficacy of stem cell transplant in patients whose primary disease or overall physical condition do not warrant this procedure.

Other Non-covered Indications

The following are considered experimental and unproven and are excluded from coverage:

- autologous stem cell transplantation for Crohn's Disease
- stem cell therapy for erectile dysfunction
- autologous bone marrow cells, including transendocardial delivery, for coronary artery disease, left ventricular dysfunction, heart failure or angina
- age-related macular degeneration
- amyotrophic lateral sclerosis
- diabetes mellitus (type I)
- essential thrombocythemia
- polycythemia vera
- recessive dystrophic epidermolysis bullosa
- retinitis pigmentosa
- thrombotic thrombocytopenic purpura
- spinal cord injury

II. CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS) COVERAGE DETERMINATION

Any applicable federal or state mandates will take precedence over this medical coverage policy.

Medicare: Refer to the CMS Online Manual System (IOMs) and Transmittals.
For the most current applicable CMS National Coverage Determination (NCD)/Local Coverage Determination (LCD)/Local Coverage Article (LCA) refer to CMS Medicare Coverage Database.

The information below is current as of the review date for this policy. However, the coverage issues and policies maintained by CMS are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. MAC jurisdiction for purposes of local coverage determinations is governed by the geographic service area where the Medicare Advantage plan is contracted to provide the service. Please refer to the Medicare Coverage Database website for the most current applicable NCD, LCD, LCA, and CMS Online Manual System/Transmittals.

National Coverage Determinations (NCDs)
NCD 110.23 – Stem Cell Transplantation
Local Coverage Determinations (LCDs)

CGS Administrators, LLC	None identified
First Coast Service Options, Inc.	None identified
National Government Services, Inc.	L39513 - Allogeneic Hematopoietic Cell Transplantation for Primary Refractory or Relapsed Hodgkin and Non-Hodgkin Lymphoma with B-cell or T-cell Origin
Noridian Healthcare Solutions	L39396 - Allogeneic Hematopoietic Cell Transplantation for Primary Refractory or Relapsed Hodgkin's and Non-Hodgkin's Lymphoma with B-cell or T-cell Origin
Novitas Solutions, Inc.	None identified
Palmetto GBA	None identified
WPS Insurance Corporation	None identified

III. BACKGROUND

Definitions

Tandem Transplantation is defined as two or more planned courses of high dose chemotherapy and stem cell support, either autologous or allogeneic. Tandem transplants are typically administered at intervals of two to six months, contingent on recovery from prior toxicity. Multiple cycles of high-dose chemotherapy with stem cell transplantation differs from tandem transplant in that more time is allowed between transplantation to permit hematopoietic recovery.

Responsive is defined as a tumor showing either a complete or partial remission.

Partial remission is defined as at least a 50% reduction in tumor burden.

Relapse is defined as a tumor recurrence after a prior complete remission

Refractory disease is a failure to attain a complete or partial response. The refractoriness can be primary (failure to respond to initial therapy) or secondary (initial response but failure to respond after disease relapse).

Myeloablative Chemotherapy is high-dose chemotherapy that kills cells in the bone marrow, including cancer cells. It lowers the number of normal blood-forming cells in the bone marrow, and can cause severe side effects. Myeloablative chemotherapy is usually followed by a bone marrow or stem cell transplant to rebuild the bone marrow.

Non-myeloablative transplants or “mini-transplants” or mini-allograft or reduced intensity conditioning transplant: lower and less toxic doses of chemotherapy and radiation are given, followed by the infusion of donor stem cells.

Sources of Stem Cells
Autologous: Stem cells may be harvested from the patient's bone marrow or more commonly, peripheral blood. Peripheral stem cells are harvested via one or more pheresis procedures. A prior course of chemotherapy (typically cyclophosphamide) or growth factors or both can increase the number of circulating stem cells.

Syngeneic: Syngeneic stem cells refer to genetically identical bone marrow or peripheral stem cells harvested from an identical twin.

Allogeneic: Allogeneic stem cell support (i.e. using stem cells from a donor) provides two theoretical advantages; the lack of tumor contamination of autologous stem cells and the possibility of a beneficial graft vs. tumor effect. Allogeneic stem cells can be harvested from either the bone marrow or peripheral blood. See policy on Non-Myeloablative Allogeneic Stem Cell Transplant.

Umbilical Cord Blood: Blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft vs. host disease.

Autologous Stem Cell Transplant for Crohn's Disease
Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD). It can affect any part of the digestive tract, from the mouth to the anus, with patterns of intestinal involvement that alternate between healthy and diseased areas. Its inflammation is associated with the appearance of transmural granulocytic infiltrates. The prevalence of CD is at an epidemiological peak in developed Western countries, with an average prevalence of 322 per 100,000 individuals in Europe, while in North America the prevalence is 319 per 100,000 individuals. Some 30% of patients diagnosed with CD are less than 20 years old. The main symptoms of CD are diarrhea, abdominal pain, rectal bleeding and weight loss. The different therapeutic options include the administration of corticosteroids in the acute phase of the disease, aminosalicylates, immunosuppressants, biological agents, and, ultimately, surgical bowel resection in the medium and long term. There are cases of refractory CD in which conventional therapies are not effective, so these patients may require surgery to remove the intestinal region affected by CD. It is estimated that 25% of CD patients are refractory to available medical and surgical treatments, compromising their quality of life. In these cases, alternative therapies, such as autologous hematopoietic stem cell transplantation (aHSCT), can be considered to induce and maintain remission. (Serrano-Fernandez et al., 2024)

A 2024 systematic review and meta analysis was carried out to evaluate the efficacy of autologous hematopoietic stem cell transplantation in inducing remission in patients with Crohn's disease. The mean and standard deviation of the Crohn's Disease Activity Index (CDAI) pre- and post- treatment were used to evaluate treatment response. A total of 12 studies including 609 records were selected for inclusion in the review. The results showed that immediate intervention proved effective in inducing a decrease in the Crohn Disease Activity Index compared to late intervention with conventional therapies. Moreover, the meta-analysis demonstrated efficacy for Crohn disease and associated fistulas with a mean decrease in the CDAI of -217.53 ± 14.3. When evaluating the efficacy of the procedure in perianal fistulas, a risk ratio of 0.47 with a 95% CI of [0.26, 0.86] was obtained. However, the procedure showed adverse effects, such as infections, acute renal failure or deaths. (Serrano-Fernandez et al., 2024)

O Lindsay and colleagues (2024) conducted an open-label, multicenter, randomized controlled trial to evaluate the safety and efficacy of autologous hematopoietic stem cell

transplantation with low-dose cyclophosphamide mobilization and reduced intensity conditioning versus standard of care in refractory Crohn's disease. 13 participants were randomized to the treatment group and 10 to the control group. In the intervention group, ten (77%) participants underwent HSCT and nine (69%) reached 48-week follow-up; in the control group, nine (90%) reached 48- week follow-up. The trial was halted in response to nine reported suspected unexpected serious adverse reactions in six (46%) patients in the intervention group, including renal failure due to proven thrombotic microangiopathy in three participants and one death due to pulmonary venoocclusive disease. At week 48, absence of endoscopic ulceration without surgery or death was reported in three (43%) of seven participants in the intervention group and in none of six participants in the control group with available data. Serious adverse events were more frequent in the intervention group (38 in 13 [100%] patients) than in the control group (16 in four [40%] patients). A second patient in the intervention group died after week 48 of respiratory and renal failure. (O Lindsay et al., 2024) This study highlights serious concerns for safety with the use of HSCT with an immune-ablative regimen of reduced intensity.

Guidelines/Position Statements

- Stem Cell Transplantation (HSCT) for Severe Autoimmune Diseases (ADs): A Position Statement From the EBMT Autoimmune Diseases Working Party (ADWP), the EBMT Nurses Group, the EBMT Patient, Family and Donor Committee and the Joint Accreditation Committee of ISCT and EBMT (JACIE) (Jessop et al., 2019)
    - "The type of HSCT almost always used in patients with severe ADs is autologous HSCT (or ‘auto-transplant’). Auto-transplant is more safely delivered compared with allogeneic HSCT (or ‘allo-transplant’), which is a much more complex procedure requiring a donor"
    - "Compared with most standard treatments, HSCT is associated with greater short-term risks, including a risk of treatment related mortality (TRM), and long-term complications (so called ‘late effects’) due to the intensity of the treatment. The risk of complications is higher with autologous HSCT in some types of diseases and in allogeneic HSCT. Risks increase with age, more advanced disease and the presence of other conditions which affect patients’ fitness. Decisions should be individualised for each patient" (p. 938).

Stem Cell Therapy For Erectile Dysfunction

Erectile dysfunction (ED) is a condition characterized by the inability to maintain an erection to achieve satisfactory sexual intercourse. It is a global male health issue which causes psychosocial impacts and significant health burdens. Erectile dysfunction can be caused by organic, psychological, and neurogenic factors, as well as hormonal disturbances and side effects of certain medications. ED typically occurs in men over 40 years old and causes serious effects on the sexual life of the patient.

Generally, the available treatment of erectile dysfunction aims to increase the ability of penile erection temporarily, although it does not provide permanent effects on the endothelial impairment or homeostasis of penile tissues. Commonly used treatments include phosphodiesterase-5 inhibitors (PDE5i), intracorporal injections, vacuum devices, and prosthesis implantation. However, these treatment options are limited by the high cost, side effects, pain, and often unsatisfactory results. (Siregar et al., 2022)

Existing treatments for ED mainly focus on symptom relief rather than addressing the underlying cause. Stem cells (SCs) have shown potential as a therapeutic approach for ED due to their anti-inflammatory properties.

In a systematic review by Siregar and colleagues (2022), the authors sought to review the available information in the literature regarding the use of stem cells in the treatment of erectile dysfunction. 9 articles including 165 patients with erectile dysfunction with various medical conditions were utilized. Several stem cell types have been used for treating erectile dysfunction, including mesenchymal stem cell, placental matrix-derived stem cell, mesenchymal stem cell-derived exosome, adipose-derived stem cell, bone marrow-derived mononuclear stem cell, and umbilical cord blood stem cell. Generally, stem cell therapy showed a good efficacy and safety profile, although not enough studies exist on the protocol, dosage, and mechanism of action. The conclusion was that stem cell therapy has a good therapeutic potential in erectile dysfunction, and the available data from the literature could be the base of usage of stem cells in the treatment of erectile dysfunction although there is a need for more research for broader usage. (Siregar et al., 2022)

Another systematic review also aimed to assess the current status of trials and determine the potential impact of SCs on male sexual health. The eligibility criteria for inclusion in this analysis focused on clinical trials involving humans that evaluated the safety and efficacy of SC therapy for ED. Exclusion criteria encompassed case reports, case series, abstracts, reviews, and editorials, as well as studies involving animals or SC derivatives. 18 articles involving 373 patients were included in the final analysis. Multiple types of SC were utilized in the treatment of ED: mesenchymal SCs, placental matrix-derived mesenchymal SCs, mesenchymal SC-derived exosomes, adipose-derived SCs, bone marrow-derived mononuclear SCs, and umbilical cord blood SCs. The authors concluded that SC therapy shows promise as an innovative and safe treatment for organic ED. However, the lack of standardized techniques and controlled groups in many studies hampers the ability to evaluate and compare trials. (Furtado et al., 2023)

Guidelines/Position Statements

- American Urological Association: Erectile Dysfunction: AUA Guideline (Burnett et al., 2018)
    - “For men with ED, intracavernosal stem cell therapy should be considered investigational” (Conditional Recommendation; Evidence Level: Grade C)
- European Association of Urology: Sexual and Reproductive Health – Management of Erectile Dysfunction (Salonia et al., 2021)
    - “The use of stem cells as a regenerative treatment for ED is currently under investigation”

Autologous Bone Marrow Cells, Including Transendocardial Delivery, for Coronary Artery Disease, Left Ventricular Dysfunction, Heart Failure or Angina

Coronary artery disease is a leading cause of death in the United States and can cause substantial damage to the heart when not fatal. Myocardial infarction (MI), a heart attack, occurs when the coronary arteries that supply blood to the heart become blocked. For acute MI, drug therapy to dissolve blood clots is the most effective immediate noninvasive treatment and it is usually given within the first 6 hours after the acute event. In some cases of coronary artery obstruction, satisfactory results can be obtained with

angioplasty, in which a small balloon is inflated within the blocked artery to reopen it. Another option is implantation of a coiled or tubular stent to help hold the artery open. Aside from angioplasty and stenting, the most common surgical procedure used to treat coronary artery disease is coronary artery bypass graft surgery. Although these procedures can restore blood flow to the heart, scarring of the heart muscle occurs due to cell death during prolonged periods of insufficient blood flow. Encouraged by evidence that limited regeneration of heart muscle occurs after MI, many researchers are attempting to enhance recovery of heart function after MI by implanting stem cells, undeveloped cells from the patient's own blood or bone marrow that can change into heart muscle cells. (Hayes, 2009) Unfortunately, there is a lack of recent high-quality literature to support the safety and efficacy of this treatment method.

Heart failure (HF) is another common condition with no curative treatment. Over the past decade, and more particularly in the past 2 years, there has been an upsurge in clinical trials investigating the effects of stem cells in patients with chronic systolic heart failure. In an attempt to determine the best strategy to improve myocardial function, several types of cells and delivery methods have been studied in patients with ischemic and nonischemic cardiomyopathy (ICM and NICM, respectively). The results of these clinical trials have been conflicting, with some showing substantial clinical improvement and others demonstrating little benefit. The heterogeneity of the reported clinical benefits seems to be related to the type of study (open-label or blinded trial) and the underlying mechanism of heart failure (ICM or NICM). (Poulin et al., 2016)

Jeyaraman et al (2017) conducted a meta-analysis to critically appraise best-available evidence on efficacy and safety of intracoronary administration of autologous bone marrow stem cell (BMSC) therapy in STEMI patients after primary percutaneous coronary intervention. 42 RCTs (3365 STEMI patients) were included. The authors found that BMSC therapy did not significantly decrease mortality (risk ratio, 0.71; 95% confidence interval, 0.45-1.11; I2, 0%; absolute risk reduction, 0.1%; 95% confidence interval, -0.71 to 0.91; 40 trials; 3289 participants; I2, 0%; low strength of evidence). BMSC therapy had no effect on secondary or adverse outcomes. Trial sequential analysis for all-cause mortality showed no evidence of a clinically important difference, with a very low probability that future studies can change the current conclusion.

Tian and colleagues (2014) conducted a systematic review and meta-analysis which included 11 randomized controlled trials and 492 participants, They found that intramyocardial bone marrow cell transplantation increased left ventricular ejection fraction (LVEF) (4.91%; 95% confidence interval [CI] 2.84%-6.99%; P<0.00001), reduced left ventricular end-systolic volume LVESV) (10.66 mL; 95% CI, -18.92 mL to -2.41 mL; P=0.01), and showed a trend toward decreased left ventricular end-diastolic volume (LVEDV) (-7.82 mL; 95% CI, -16.36 mL-0.71 mL; P=0.07). Patients suitable for revascularization with coronary artery bypass grafting had greater improvement in LVEF (7.60%; 95% CI, 4.74%-10.46%, , P<0.00001). LVEDV reduction was also more significant in revascularizable ischemic heart disease (IHD) (-16.51 mL; 95% CI, -22.05 mL to - 10.07 mL; P<0.00001) than non-revascularizable IHD (-0.89 mL; 95% CI, -8.44 mL-6.66 mL; P=0.82). The authors concluded that intramyocardial bone marrow cell injection contributes to improvement in left ventricular dysfunction and reduction in left ventricular volume. Patients with revascularizable IHD may benefit more from this therapy.

In another meta-analysis that aimed to investigate the efficacy and safety of bone marrow cell (BMC) therapy on global left ventricular function in acute myocardial infarction., 6 randomized controlled trials that comprised 517 patients were included. Compared with the control groups, BMC therapy produced a slight improvement of the follow-up left ventricular ejection fraction (LVEF) [2.53%, 95% confidence interval (CI): 0.67-4.39, P=0.008] between 3 and 6 months. Similarly, BMC therapy also significantly improved the LVEF change from baseline to followup [2.88%, 95%CI: 1.69-4.08, P=0.000] compared to control groups, and the heterogeneity across the studies with regards to the follow-up LVEF (P=0.696) and the LVEF change (P=0.179). Major adverse cardiovascular events, including ventricular arrhythmia, rehospitalization for heart failure, and the composite of other cardiovascular events (cardiac death, recurrent myocardial infarction, infarct-vessel revascularization procedure, and stroke), were not significantly different between BMC therapy and control groups [relative risk (RR): 1.19, 95%CI: 0.68-2.06; RR: 1.79, 95%CI: 0.62-5.17; and RR: 1.05, 95%CI: 0.81-1.35, respectively]. The authors concluded that intracoronary BMC infusion in patients with AMI seems to be safe and associated with slight improvement of the left ventricular ejection fraction at 3-6 months' follow-up. (Kang et al., 2008)

A 2016 systematic review including 29 studies aimed to evaluate the efficacy of stem cell therapy for systolic heart failure. The majority of the 29 published studies demonstrated clinical benefits of autologous bone marrow-derived mesenchymal stem cells (BM-MSCs). Left ventricular ejection fraction (LVEF) was improved in the majority of trials after therapy. Cell delivery combined with coronary artery bypass grafting was associated with the greatest improvement in LVEF. Left ventricular end-systolic volume (or diameter), New York Heart Association functional classification, quality of life, and exercise capacity were also improved in most studies after cell therapy. Most ischemic cardiomyopathy trials demonstrated a significant improvement in perfusion defects, infarct size, and myocardial viability. The authors concluded that more data are required from larger blinded trials to determine which combination of cell type and delivery mode will yield the most benefit with avoidance of harm in these patient populations. (Poulin et al., 2016)

Stem Cell Transplant for Age-Related Macular Degeneration
Age-related macular degeneration (AMD) is an ophthalmic disease that causes progressive damage to the macula, leading to irreversible vision loss and blindness. In 2020, AMD was estimated to affect 196 million people globally. AMD is characterized by the accumulation of extracellular deposits, known as drusen, accompanied by the progressive degeneration of photoreceptors and adjacent tissues. Disease progression is associated with chronic inflammation, retinal cell metabolic rate reduction, oxidative stress, and extracellular matrix reduction, resulting in a gradual and progressive degeneration and the loss of the retinal pigment epithelium (RPE) cells initially, followed by that of photoreceptors and adjacent tissues. Over time, if inflammation persists and complement levels increase, neovascular damage results in fluid leakage or hemorrhage from the highly permeable subretinal or sub-RPE vascular networks. Multiple factors (ageing, diet, smoking, genetics, and other environmental factors) increase the risk of AMD. Dietary supplementation of formulations with antioxidant and antiinflammatory properties is recommended. In general, the functional improvement is modest and short term, but these formulations may slow down disease progression in the early and intermediate stages. Previously, photodynamic therapy was used for the treatment of wet AMD; however, the current approach to treatment involves monoclonal antibodies

that act on vascular endothelial growth factor (VEGF) receptors, and which are administered via an intravitreal injection. However, anti-VEGF therapy does not counteract the underlying atrophic mechanisms, and AMD continues to progress. There is currently no effective treatment for dry AMD. Stem cell therapy is being studied as a treatment for AMD. (Li et al., 2022)

In a 2022 systematic review and meta-analysis, the rates of visual acuity outcomes and adverse events associated with stem cell transplantation were examined. The analysis examined 10 studies (102 patients), including one and three, randomized and non-randomized clinical trials, and one and five, multicenter prospective and prospective clinical trials, respectively. Metaanalysis showed changes in best-corrected visual acuity in the study eyes after stem cell transplantation (6 months: risk ratio [RR] = 17.00, 95% confidence interval [CI] 6.08-47.56, P < 0.00001; 12 months: RR = 11.00, 95% CI 2.36-51.36, P = 0.002). Subgroup analysis showed that different stem cell types achieved better best-corrected visual acuity at post-operative 6 months, compared to that observed at baseline. Four cases of related ocular adverse events and no related systemic adverse events were reported. The authors concluded that stem cell transplantation may improve best-corrected visual acuity in dry age-related macular degeneration, based on small sample sizes and fewer randomised controlled trials. (Li et al., 2022)

Stem Cell Transplant for Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by loss of upper and lower motor neurons, resulting in worsening weakness of voluntary muscles. ALS inevitably leads to paralysis, respiratory insufficiency, and eventually death. The overall prevalence and incidence of ALS are estimated at 4.42 per 100,000 and 1.59 per 100,000, respectively. The underlying pathophysiological mechanisms for ALS have been a topic of extensive research. Stem cell (SC) therapy is considered one of the most promising therapeutic approaches for ALS. With this therapy, various pathogenic mechanisms could be targeted to slow the progression of the disease. SC therapy could provide both trophic and immunomodulatory support and potentially allow for the regeneration of motor neurons. (Aljabri et al., 2021)

In a 2016 meta-analysis, stem cell therapy and survival in animal models and patients with ALS was studied using preclinical in vivo and retrospective clinical studies. Meta-analysis of the data confirmed the efficacy of stem cell therapy in improving survival in preclinical trials, where a mean difference of 9.79 days (95% confidence interval: 4.45 - 15.14) in lifespan favored stem cell therapy. The authors did note that the number of clinical studies is still insufficient to assess their effectiveness, and these studies only demonstrate the absence of serious adverse events. They also pointed out that even this conclusion should be interpreted with caution because clinical studies are retrospective and heterogeneous and have an unsatisfactory quality. (Conceiacao Moura et al., 2016)

Another meta-analysis by Abduh Wahid and colleagues (2019) aimed to assess the effects of cell-based therapy for people with ALS/motor neuron disease (MND), compared with placebo or no treatment. Two randomized controlled trials involving 112 patients were included in the review. One study compared autologous bone marrow-

mesenchymal stem cells (BM-MSC) plus riluzole versus control (riluzole only), while the other study compared combined intramuscular and intrathecal administration of autologous mesenchymal stem cells secreting neurotrophic factors (MSC-NTF) to placebo. The latter study was reported as an abstract and provided no numerical data. The only study that contributed to the outcome data in the review involved 64 participants, comparing BM-MSC plus riluzole versus control (riluzole only). It reported outcomes after four to six months. The certainty of evidence was low for all major efficacy outcomes, with imprecision as the main downgrading factor, because the range of plausible estimates, as shown by the 95% confidence intervals (CIs), encompassed a range that would likely result in different clinical decisions. Functional impairment, expressed as the mean change in the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) score from baseline to six months after cell injection was slightly reduced (better) in the BM-MSC group compared to the control group (mean difference (MD) 3.38, 95% CI 1.22 to 5.54; 1 RCT, 56 participants; low-certainty evidence). ALSFRS-R has a range from 48 (normal) to 0 (maximally impaired); a change of 4 or more points is considered clinically important. The trial did not report outcomes at 12 months. There was no clear difference between the BM-MSC and the no treatment group in change in respiratory function (per cent predicted forced vital capacity; FVC%; MD -0.53, 95% CI -5.37 to 4.31; 1 RCT, 56 participants; low-certainty evidence); overall survival at six months (risk ratio (RR) 1.07, 95% CI 0.94 to 1.22; 1 RCT, 64 participants; low-certainty evidence); risk of total adverse events (RR 0.86, 95% CI 0.62 to 1.19; 1 RCT, 64 participants; low-certainty evidence) or serious adverse events (RR 0.47, 95% CI 0.13 to 1.72; 1 RCT, 64 participants; low-certainty evidence). The study did not measure muscle strength. The conclusion of this meta-analysis was that there is a lack of high-certainty evidence to guide practice on the use of cell-based therapy to treat ALS/MND. Uncertainties remain as to whether this mode of therapy is capable of restoring muscle function, slowing disease progression, and improving survival in people with ALS/MND. (Abdul Wahid et al., 2019)

Stem Cell Transplant for Multiple Sclerosis

Multiple sclerosis (MS) is characterized by chronic inflammation, neurodegeneration, and immune-mediated responses of the central nervous system (CNS), leading to demyelination, gliosis, and axonal damage. MS can cause permanent disability, reduce the quality of life, and shorten life span. (Nabizadeh et al., 2022) It presents with different manifestations such as visual loss, weakness, sensory, and even sphincteric disturbances. MS includes five main clinical courses: Primary Progressive Multiple Sclerosis (PPMS), Secondary Progressive Multiple Sclerosis (SPMS), Relapsing–Remitting Multiple Sclerosis (RRMS), Clinically Isolated Syndrome (CIS), and Radiologically Isolated Syndrome (RIS). These clinical phenotypes are assessed according to two descriptors: disease activity and progression. Disease activity is evidenced by clinical relapses or lesions activity on MRI, while disability progression is associated with increasing neurological dysfunction. Currently, approved medications for MS only aim to alleviate the symptoms or slow disease progression and reduce relapses through disease-modifying therapies (DMTs). Patients with SPMS and PPMS have fewer options for medications with limited efficacy and safety issues. Stem cell transplantation (SCT) has emerged as another treatment option for multiple sclerosis in addition to different autoimmune neurological diseases. SCT involves ablation of the patient's aberrant immune system and reconstitution of a new immune system derived after the infusion of healthy stem cells. The European Group for Blood and Marrow Transplantation has recommended autologous hematopoietic SCT (AHSCT) for MS

patients showing inflammatory disease activity, including RRMS patients not responding to the approved DMTs and SPMS patients with worsening disability. Young and ambulatory MS patients are considered the optimal candidates for AHSCT. (Nawar et al., 2024)

In an open-label randomized, multicenter clinical trial, Burt and colleagues (2019) sought to study the effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis. A total of 110 patients with RRMS were included in the study and randomized to receive HSCT along with cyclophosphamide (200 mg/kg) and antithymocyte globulin (6 mg/kg) (n = 55) or DMT of higher efficacy or a different class than DMT taken during the previous year (n = 55). The primary end point was disease progression, defined as an EDSS score increase after at least 1 year of 1.0 point or more (minimal clinically important difference, 0.5) on 2 evaluations 6 months apart, with differences in time to progression estimated as hazard ratios. Among 110 randomized patients (73 [66%] women; mean age, 36 [SD, 8.6] years), 103 remained in the trial, with 98 evaluated at 1 year and 23 evaluated yearly for 5 years (median follow-up, 2 years; mean, 2.8 years). The authors found that disease progression occurred in 3 patients in the HSCT group and 34 patients in the DMT group. Median time to progression could not be calculated in the HSCT group because of too few events; it was 24 months (interquartile range, 18-48 months) in the DMT group (hazard ratio, 0.07; 95% CI, 0.02-0.24; P < .001). During the first year, mean EDSS scores decreased (improved) from 3.38 to 2.36 in the HSCT group and increased (worsened) from 3.31 to 3.98 in the DMT group (between-group mean difference, −1.7; 95% CI, −2.03 to −1.29; ; P < .001). There were no deaths and no patients who received HSCT developed nonhematopoietic grade 4 toxicities (such as myocardial infarction, sepsis, or other disabling or potential life-threatening events). (Burt et al., 2019)

In a 2024 systematic review and meta-analysis, the clinical efficacy and safety stem cell transplantation in MS patients was reviewed. 9 randomized controlled trials, including 422 patients, were included. The results showed that SCT significantly improved patients expanded disability status scale after 2 months (N = 39, MD = - 0.57, 95% CI [- 1.08, - 0.06], p = 0.03). SCT also reduced brain lesion volume (N = 136, MD = - 7.05, 95% CI [- 10.69, - 3.4], p = 0.0002). The effect on EDSS at 6 and 12 months, timed 25-foot walk (T25-FW), and brain lesions number was nonsignificant. Significant adverse events (AEs) included local reactions at MSCs infusion site (N = 25, RR = 2.55, 95% CI [1.08, 6.03], p = 0.034) and hematological disorders in patients received immunosuppression and autologous hematopoietic SCT (AHSCT) (N = 16, RR = 2.33, 95% CI [1.23, 4.39], p = 0.009). The authors concluded that SCT can improve the disability of MS patients and reduce their brain lesion volume. The transplantation was generally safe and tolerated, with no mortality or significant serious AEs, except for infusion site reactions after mesenchymal SCT and hematological AEs after AHSCT. (Nawar et al., 2024)
Another systematic review and meta-analysis published in 2022 sought to investigating the safety and efficacy of autologous hematopoietic stem cell transplantation in patients with multiple sclerosis. 50 studies with a total of 4831 patients with MS were included. Analysis showed a significant decrease in EDSS score after treatment (standardized mean difference [SMD]: -0.48, 95% CI -0.75, -0.22). Moreover, the annualized relapse rate was also significantly reduced after AHSCT compared to the pretreatment period (SMD: -1.58, 95% CI -2.34, -0.78). The pooled estimate of progression-free survival after treatment was 73% (95% CI 69%, 77). Furthermore, 81% of patients with MS who

received AHSCT remained relapse-free (95% CI 76%, 86%). Investigating event-free survival, which reflects the absence of any disease-related event, showed a pooled estimate of 63% (95% CI 54%, 73%). Also, the MRI activity-free survival was 89% (95% CI 84%) among included studies with low heterogeneity. New MRI lesions seemed to appear in nearly 8% of patients who underwent AHSCT (95% CI 4%, 12%). The meta-analysis showed that 68% of patients with MS experience no evidence of disease activity (NEDA) after AHSCT (95% CI 59%, 77). The overall survival after transplantation was 94% (95% CI 91%, 96%). In addition, 4% of patients died from transplant-related causes (95% CI 2%, 6%). The authors concluded that current data encourages a broader application of AHSCT for treating patients with MS while still considering proper patient selection and transplant methods. In addition, with increasing knowledge and expertise in the field of stem-cell therapy, AHSCT has become a safer treatment approach for MS. (Nabizadeh et al., 2022)

Guidelines/Position Statements

- American Society for Transplantation and Cellular Therapy (ASTCT) - *Autologous Hematopoietic Cell Transplantation for Treatment-Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation* (Cohen et al., 2019)
    - "The [American Society Blood and Marrow Transplantation] Task Force recommends revising the recommended indication for [AHSCT] in MS to 'standard of care, clinical evidence available', for patients with relapsing forms of MS (RRMS or [PPMS] with superimposed activity) who have prognostic factors that indicate a high risk of future disability, including ongoing clinical relapse or MRI lesion activity despite treatment with available DMTs, especially if disease activity continues despite treatment with high-efficacy DMTs and/or worsening disability" (p. 851).
- European Society for Blood and Marrow Transplantation - *Autologous Haematopoietic Stem Cell Transplantation and Other Cellular Therapy in Multiple Sclerosis and Immune-mediated Neurological Diseases: Updated Guidelines and Recommendations From the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE)* (Sharrack et al., 2020)
    - "AHSCT should be offered to patients with RRMS with high clinical and MRI inflammatory disease activity … despite the use of one or more lines of approved DMTs. Evidence best supports treatment in patients who are able to ambulate independently (EDSS 5.5 or less), who are younger than 45 years and have disease duration less than 10 years (level S/I)" (p. 289).
    - "Patients with ‘aggressive’ MS, who develop severe disability in the previous 12 months, are suitable candidates for AHSCT. Given the potential for irreversible disability, such patients may be considered even before failing a full course of DMT (level CO/II)" (p. 289).
    - "Patients with SPMS should be considered for AHSCT, preferably in a prospective clinical trial, only when inflammatory activity is still evident (clinical relapses and Gd-enhancing or new T2 MRI lesions) with documented disability progression in the previous 12 months (level CO/II)" (p. 289).
    - "Patients with PPMS should be considered for AHSCT, preferably in a prospective clinical trial, only when inflammatory activity is evident (Gd-

enhancing and new T2 MRI lesions) with documented evident disability progression in the previous 12 months (level CO/II)" (p. 289).
    - "Paediatric patients with MS who have breakthrough inflammatory disease with less toxic treatments may be considered for AHSCT (level CO/II)" (p. 289).
- National Multiple Sclerosis Society (NMSS) - Autologous Hematopoietic Stem Cell Transplant in Multiple Sclerosis Recommendations of the National Multiple Sclerosis Society (Miller et al., 2021)
    - " … AHSCT may be a useful treatment option for people with MS who demonstrate substantial breakthrough disease activity (new inflammatory central nervous system lesions and/or clinical relapses) despite treatment with high-efficacy DMT or have contraindications to high-efficacy DMTs and are younger than 50 years, with disease duration less than 10 years" (p. 245).

Stem Cell Transplant for Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disease, and immune attacks lead to the destruction of islet cells, causing islet inflammation associated with absolute insulin deficiency. Eventually, various related complications occur, causing serious harm to the patient and negative effects on the patient's quality of life and longevity. Islet transplantation can theoretically cure diabetes, but it is limited by a lack of donor sources and susceptible to immune rejection complications and difficulties related to the separation of the pancreatic islets. In recent years, stem cell-based transplantation has been explored for the treatment of diabetes. Unlike embryonic stem cells, the use of mesenchymal stem cells (MSCs) in the treatment of diabetes does not involve tumorigenic risks or ethical issues. MSC transplantation is an attractive option due to its wide range of sources, easy access, self-renewal ability, multi-differentiation potential, low immunogenicity, secretion of various cytokines, and other biological characteristics, and it is not ethically controversial. (Li et al., 2021).

Li and colleagues conducted a meta-analysis including 10 studies (4 included T1DM patients) with 239 participants total to examine the efficacy of mesenchymal stem cells (MSCs) therapy in the treatment of diabetes mellitus. According to the pooled estimates, the glycated hemoglobin (HbA1c) level of the MSC-treated group was significantly lower than it was at baseline (mean difference (MD) = −1.51, 95% CI −2.42 to −0.60, P = 0.001). The fasting C-peptide level of the MSC-treated group with T1DM was higher than that of the control group (SMD = 0.89, 95% CI 0.36 to 1.42, P = 0.001), and their insulin requirement was significantly lower than it was at baseline (SMD = −1.14, 95% CI −1.52 to −0.77, P < 0.00001). The authors concluded that transplantation of mesenchymal stem cells has beneficial effects on diabetes mellitus, especially T1DM, with no obvious adverse reactions.

Another meta-analysis by Santos Pires and colleagues (2022) included 38 original articles, which included 647 control cases and 654 treatments with three-, six- and twelve-month follow-ups of T1DM and T2DM patients. The efficacy of stem cell therapy was validated by comparing laboratory parameters such as fasting blood glucose and C-peptide levels before and after treatment. The results found that stem cell (SC) treatments significantly reduced the need for insulin following six and twelve months of treatment, whereas there was no significant decrease after three months. Fasting blood

glucose and glycosylated hemoglobin levels were significantly reduced in all follow-ups with SC. In addition, SC treatment caused a significant increase in C-peptide levels. Bone marrow hematopoietic stem cell therapy produced better results than the conventional drug treatment for diabetes mellitus (semagglutide).

Stem cell transplantation for the treatment of type 1 diabetes mellitus remains an area of investigation. In an UpToDate article on type 1 diabetes mellitus: prevention and disease-modifying therapy, a section on therapies without demonstrated benefit after clinical diagnosis states that autologous hematopoietic stem cell transplantation (HSCT) entails ex vivo expansion of pluripotent stem cells with subsequent infusion into a patient who has undergone nonmyeloablative chemotherapeutic conditioning. Although therapy confers a high rate of insulin independence, the conditioning component of HSCT imparts significant risks, including life-threatening bone marrow aplasia and sepsis. These risks render HSCT unlikely to be useful in type 1 diabetes. (UpToDate, 2025)

Guidelines/Position Statements

- American Diabetes Association: The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (2021)
    - This guideline briefly mentions that stem cells are under investigation to solve the problem of limited availability of donors for pancreas or islet transplantation but does not provide a formal recommendation for or against this treatment.

Stem Cell Transplant for Essential Thrombocythemia and Polycythemia Vera

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm characterized by sustained thrombocytosis in the peripheral blood and increased numbers of megakaryocytes in the bone marrow (1). ET has a long symptom-free period with the absence of life-threatening thromboembolic or hemorrhagic events. However, myelofibrosis occurs in about 10% of patients with a diagnosis of ET. (Murata et al., 2020) Current drug therapy for post-ET and postpolycythemia vera (PV) myelofibrosis is not curative and unlikely to prolong survival. The only potentially curative therapy for secondary myelofibrosis is allogeneic hematopoietic stem cell transplantation (HSCT). Despite this, there are few reports focusing on the outcomes of HSCT for patients with post-ET and post-PV myelofibrosis.

Polycythemia vera (PV) is another chronic myeloproliferative neoplasm characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis (3). The major symptoms of PV are related to hypertension or vascular abnormalities caused by the increased red blood cell mass. The incidence of myelofibrosis in patients with a diagnosis of PV is reported to be about 10-20%. (Murata et al., 2020)

Murata et al (2020) conducted a retrospective study to analyze the clinical outcomes of HSCT for post-ET and post-PV myelofibrosis. Clinical data for patients with post-ET (n=29) and post-PV (n=9) myelofibrosis who had received first allogeneic HSCT were extracted from the Transplant Registry Unified Management Program, which is a registry of the outcomes of HSCT in Japan. Within the cohort, five patients died without neutrophil recovery within 60 days after transplantation. The incidence of neutrophil recovery was significantly lower in umbilical cord blood (UCB) transplantation than in related donor transplantation (40% vs. 92%, p=0.010). The 1-year non-relapse mortality for post-ET and post-PV myelofibrosis was 35% and 27%, respectively (p=0.972). No patient or transplantation characteristics were associated with non-relapse mortality. The 4-year overall survival for post-ET and post-PV myelofibrosis was 46%

and 65%, respectively (p=0.362). A univariate analysis identified UCB transplantation (vs. related donor, p=0.017) and ≥10 times red blood cell transfusions before transplantation (vs. <10 times, p=0.037) as predictive of a lower overall survival. The authors concluded that Allogeneic HSCT provides a long-term survival for at least some patients with post-ET and post-PV myelofibrosis. Further studies with more patients are required to determine the best alternative donor.

Stem Cell Transplant for Recessive Dystrophic Epidermolysis Bullosa

Recessive dystrophic epidermolysis bullosa (RDEB) is an incurable disease that causes severe mucocutaneous fragility due to mutations in COL7A1 (encoding type VII collagen [C7]). RDEB is one of the most severe forms of EB; it is characterized by recurrent blistering, chronic wounds, disabling scarring in the skin, and mucosa and internal organ dysfunctions, leading to substantial morbidity and mortality. Currently, there is no cure for this severe subtype of epidermolysis bullosa (EB); however, novel therapeutic strategies have been developed in the fields of gene and cell therapies. Mesenchymal stem cells (MSCs) have been identified as an option for allogeneic cell therapy for RDEB based on their potential mechanisms of action, including immunomodulation, migration to damaged tissue, stimulation of tissue regeneration, and reduction of fibrosis, mainly through paracrine activities (Eun Lee et al., 2021) Unfortunately, there is a dearth of high-quality data support this treatment option.

In an early phase I/IIa trial, the safety and possible clinical efficacy of intravenous infusion of allogeneic human umbilical cord blood–derived mesenchymal stem cells (hUCB-MSCs) in patients with RDEB was evaluated. Four adult and two pediatric patients with RDEB were treated with 3 intravenous injections of hUCB-MSCs (1 × 106 to 3 × 106 cells/kg) every 2 weeks and followed up for 8–24 months after treatment. The primary endpoint was safety. Secondary endpoints related to efficacy included clinical parameters, such as disease severity score, wound assessment, itch and pain score, and quality of life. C7 expression levels and inflammatory infiltrates in the skin, as well as serum levels of inflammatory markers and neuropeptides, were also assessed. The results showed that intravenous hUCB-MSC infusions were well tolerated, without serious adverse events. Improvements in the Birmingham Epidermolysis Bullosa Severity Score, body surface area involvement, blister counts, pain, pruritus, and quality of life were observed with maximal effects at 56–112 days after treatment. hUCB-MSC administration induced M2 macrophage polarization and reduced mast cell infiltration in RDEB skin. Serum levels of substance P were decreased after therapy. Increased C7 expression was observed at the dermoepidermal junction in 1 of 6 patients at day 56. This study demonstrates relative safety and possible transient clinical benefit of stem cell therapy for RDEB. (Eun Lee et al., 2021)

A systematic review was conducted to examine the effects of bone marrow transplantation and bone marrow-derived mesenchymal stem cell therapy in epidermolysis bullosa. 12 studies involving 55 EB patients were included. Three were retrospective cohort studies, three were clinical trials, and two were case series; the other four were case reports. Patients with severe forms of EB that underwent BMT and/or BM-MSCs were included, with recessive dystrophic EB as the most common EB type. 53 (96.4%) patients had better wound healing, and 3 (5.5%) patients died of sepsis. The most common adverse events reported were graft failure, sepsis, graft-versus-host disease, and renal insufficiency. The authors concluded that allogeneic BMT is a high-risk procedure with possible benefits and adverse events. BM-MSCs revealed favorable outcomes to improve the safety of EB cell-based therapy by minimizing the risk of serious adverse events, reducing blisters, and accelerating wound healing; but further studies are needed to assess the treatment's long-term effects and clarify the risk/benefit ratio of procedure versus conventional therapy. (Agustin et al., 2024)

Stem Cell Transplant for Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a group of hereditary retinal dystrophies characterized by progressive degeneration of photoreceptor cells, which results in debilitating visual impairment. The hallmark clinical features of RP typically manifest as night blindness, followed by gradual constriction of the visual field, decreased visual acuity, and, in some cases, the eventual loss of central vision. The prognosis for individuals affected by RP varies widely based on genetic subtype, age of onset, and the rate of disease progression. Despite decades of research and considerable advancements in understanding the molecular mechanisms underpinning RP, efficacious treatment options still need to be discovered. Traditional management strategies have primarily focused on supportive measures to preserve existing vision and enhance visual function through low-vision aids and adaptive techniques. However, these interventions do not alter the natural course of the disease nor halt its progression. (Confalonieri et al., 2024)

In a 2025 systematic review and meta-analysis by Krungkraipetch and colleagues, the efficacy and safety of mesenchymal stem cell therapies in retinitis pigmentosa was reviewed. Outcomes of interest included best-corrected visual acuity (BCVA), central macular thickness, retinal sensitivity, quality of life, and safety profiles. Eleven studies involving 355 RP patients were included. Umbilical cord-derived MSCs and bone marrow-derived MSCs demonstrated significant short-term improvements in BCVA and retinal function. Subretinal and suprachoroidal delivery methods were associated with better outcomes compared to systemic infusion. Adverse effects were minimal, with transient inflammation being the most reported. The duration of benefits varied, with most studies reporting sustained improvements up to 12 months, while long-term efficacy beyond this period was less conclusive. The conclusion was that MSC therapies show promise in improving visual function and retinal health, with safety profiles supporting their clinical feasibility. However, differences in administration methods and MSC types influence outcomes. Further large-scale, long-term randomized controlled trials are needed to optimize treatment protocols and validate sustained benefits. (Krungkraipetch et al., 2025)

Stem Cell Transplant for Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy (TMA), primarily caused by a deficiency in the von Willebrand factor (VWF)-cleaving enzyme ADAMTS13 (A disintegrin and metalloproteinase with thrombospondin motifs 13). This deficiency can be the result of mutations in the ADAMTS13 gene (hereditary/congenital TTP; cTTP) or, more commonly, result from ADAMTS13 autoantibodies (acquired/immune TTP; iTTP). Acute episodes are considered a true medical emergency and are associated with a mortality rate of >90% if left untreated. Damage to major organs may also result in transient ischemic attack, stroke, myocardial infarction, or acute kidney injury. Triggers for acute episodes include infections, pregnancy, autoimmune disease, blood/marrow transplant and exposure to certain medications. The annual incidence of TTP is estimated to range between 2–6 and 3–11 cases per million persons. The current standard of care for managing acute TTP episodes is to restore ADAMTS13 levels using plasma therapy, either by plasma infusion for cTTP or plasma exchange (PEX) for iTTP. Immunosuppressive or anti-CD20 therapy (eg rituximab) and anti-VWF therapy (caplacizumab) are also options for iTTP, while prophylaxis with regular plasma infusions has been used to prevent acute episodes in cTTP. However, TTP treatment guidelines highlight a lack of high-quality evidence supporting long-term outcomes with currently available therapy. (Du et al., 2024) Stem cell therapy has been proposed as a treatment option; however given the rarity of this condition there is a lack of recent evidence to support its use for thrombotic thrombocytic purpura.

IV. GUIDELINES / POSITION STATEMENTS

Medical/Professional Society	Guideline
European Society for Blood and Marrow Transplantation	The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies (2024)
National Comprehensive Cancer Network (NCCN)	Hematopoietic Cell Transplantation (2026)
American Society for Transplantation and Cellular Therapy (ASTCT)	ASTCT Practice Guidelines (Ongoing; current updates 2024–2026)
European Society for Blood and Marrow Transplantation (EBMT)	Indications for Haematopoietic Cell Transplantation and CAR-T for Haematological Diseases, Solid Tumours and Immune Disorders (2025)
National Comprehensive Cancer Network (NCCN)	Acute Myeloid Leukemia (2026)
European Committee for Treatment and Research in Multiple Sclerosis and European Society for Blood and Marrow Transplantation	Recommendations for Autologous HSCT in Multiple Sclerosis and NMOSD (2025)
National Comprehensive Cancer Network (NCCN)	Acute Lymphoblastic Leukemia (2026)
National Comprehensive Cancer Network (NCCN)	Myelodysplastic Syndromes (2026)
National Comprehensive Cancer Network (NCCN)	Myeloproliferative Neoplasms (2025)
National Comprehensive Cancer Network (NCCN)	Chronic Myeloid Leukemia (2026)
National Comprehensive Cancer Network (NCCN)	Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma (2026)
National Comprehensive Cancer Network (NCCN)	Non-Hodgkin Lymphomas (B-Cell) (2025)
National Comprehensive Cancer Network (NCCN)	T-Cell Lymphomas (2025)
National Comprehensive Cancer Network (NCCN)	Hodgkin Lymphoma (2026)
National Comprehensive Cancer Network (NCCN)	Multiple Myeloma (2025)
National Comprehensive Cancer Network (NCCN)	Systemic Light Chain Amyloidosis (2026)
National Comprehensive Cancer Network (NCCN)	Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma (2025)
National Comprehensive Cancer Network (NCCN)	Hairy Cell Leukemia (2025)

V. REGULATORY (US FOOD AND DRUG ADMINISTRATION)

See U.S. Food & Drug Administration (FDA) Medical Device Databases for the most current information.

Device	Premarket Approval, 513(f)(2)(De Novo), or 510(k) Number	Notice date

VI. CODING

ICD-10 Codes that may support medical necessity (list not all inclusive):

C40.00 – C40.92	Malignant neoplasm of bone and articular cartilage of limbs (Ewings's sarcoma)
C56.1 – C56.9	Malignant neoplasm of ovary
C62.0 – C62.92	Malignant neoplasm of testis
C64.1 – C64.9	Malignant neoplasm of kidney, except renal pelvis (Wilms tumor)
C69.20 – C69.22	Malignant neoplasm of retina
C71.0 – C71.9	Malignant neoplasm of brain
C81.00 – C81.99	Hodgkin lymphoma
C82.00 – C82.99	Follicular lymphoma
C83.00 – C83.99	Small cell B-cell lymphoma
C84.60 – C84.69	Anaplastic large cell lymphoma, ALK-positive
C84.70 – C84.7A	Anaplastic large cell lymphoma, ALK-negative
C84.A0 – C84.A9	Cutaneous T-cell lymphoma, unspecified
C84.Z0 – C84.Z9	Other Mature T/NK-cell lymphomas,
C84.90 – C84.99	Mature T/NK-cell lymphomas, unspecified
C85.10 – C85.99	Other specified and unspecified types of non-Hodgkin lymphoma
C86.0 – C86.6	Other specified types of T/NK-cell lymphoma
C88.4x	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C88.8x	Other malignant immunoproliferative diseases
C88.9	Malignant immunoproliferative disease, unspecified
C90.00 – C90.32	Multiple myeloma and malignant plasma cell neoplasms
C91.00 – C91.Z2	Lymphoid leukemia
C92.00 – C92.Z2	Myeloid leukemia
C93.00 – C93.Z2	Monocytic leukemia
C94.00 – C94.82	Other leukemias of specified cell type
C95.00 – C95.92	Leukemia of unspecified cell type
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D46.0 – D46.9	Myelodysplastic syndromes
D56.1	Beta thalassemia
D61.01 – D61.9	Other aplastic anemias and other bone marrow failure syndromes
D64.0 – D64.4	Sideroblastic anemias
D70.0	Congenital agranulocytosis
D81.0 – D81.7	Severe combined immunodeficiencies
D82.0	Wiskott-Aldrich syndrome
D82.3	Immunodeficiency following hereditary defective response to

	Epstein-Barr virus
D84.0	Lymphocyte function antigen-1 [LFA-1] defect
D89.9	Disorder involving the immune mechanism, unspecified
E70.330	Chediak-Higashi syndrome
E75.00 – E75.6	Disorders of sphingolipid metabolism and other lipid storage disorders
E76.01 – E76.03	Mucopolysaccharidosis, type I
E85.0 – E85.9	Amyloidosis
Z48.290	Encounter for aftercare following bone marrow transplant
Z94.81	Bone marrow transplant status
Z94.89	Stem cells transplant status

ICD-10 Codes that may apply

C11.0 – C11.9	Malignant neoplasm of nasopharynx
C15.3 – C15.9	Malignant neoplasm of esophagus
C16.0 – C16.9	Malignant neoplasm of stomach
C18.0 – C20	Malignant neoplasm of the colon
C23	Malignant neoplasm of gallbladder
C24.0 – C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C25.0 – C25.9	Malignant neoplasm of pancreas
C31.0 – C31.9	Malignant neoplasm of accessory sinuses
C34.00 – C34.92	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C43.0 – C43.8	Malignant melanoma of skin
C49.0 – C49.A9	Malignant neoplasm of other connective and soft tissue
C50.011- C50.929	Malignant neoplasm, breast
C53.0 – C53.9	Malignant neoplasm of cervix uteri
C54.0 – C55	Malignant neoplasm of the uterus
C56.1 – C56.9	Malignant neoplasm of ovary
C64.1 – C64.9	Malignant neoplasm of kidney, except renal pelvis
C65.1 – C65.9	Malignant neoplasm of renal pelvis
C71.0 – C71.9	Malignant neoplasm of brain
C73	Malignant neoplasm of thyroid gland
D00.0 – D00.2	Carcinoma in situ of oral cavity, esophagus and stomach
D03.0 – D03.9	Melanoma in situ
D06.0 – D06.9	Carcinoma in situ of cervix uteri
D45	Polycythemia vera
D59.0	Drug-induced autoimmune hemolytic anemia - Use additional code for adverse effect, if applicable, to identify drug
D59.1X	Other autoimmune hemolytic anemias
D65	Disseminated intravascular coagulation [defibrination syndrome]
E10.10 – E10.9	Type I diabetes mellitus
G35	Multiple sclerosis
G36.0	Neuromyelitis optica [Devic]
H35.52	Pigmentary retinal dystrophy

I20.0 – I20.9	Angina pectoris
I24.0 – I24.9	Other acute ischemic heart diseases
I25.10 – I25.9	Chronic ischemic heart disease
K50.00 – K50.919	Crohn's disease [regional enteritits]
K51.00 – K51.919	Ulceratvie colitis
K74.0X	Hepatic fibrosis
K74.60	Unspecified cirrhosis of liver
K74.69	Other cirrhosis of liver
K75.4	Autoimmune hepatitis
K90.0	Celiac disease
L53.8	Other specified erythematous conditions
L90.0	Lichen sclerosus et atrophicus
L94.0	Localized scleroderma [morphea]
L94.1	Linear scleroderma
L94.3	Sclerodactyly
M05.00 – M05.9	Rheumatoid arthritis with rheumatoid factor
M08.00 – M08.99	Juvenile arthritis
M31.1X	Thrombotic microangiopathy
M32.0 – M32.9	Systemic lupus erythematosus (SLE)
M33.00 – M33.99	Dermatopolymyositis
M34.0 – M34.9	Systemic sclerosis [scleroderma]
N52.0 – N52.9	Male erectile dysfunction
Q81.0 – Q81.9	Epidermolysis bullosa
S14.0xxA - S14.9xxS	Injury of nerves and spinal cord at neck level
S24.0xxA - S24.9xxS	Injury of nerves and spinal cord at thorax level
S34.01xA - S34.9xxS	Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level

CPT/HCPCS Codes

* No prior authorization required for In-Network providers

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

38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions
38243*	Hematopoietic progenitor cell (HPC); HPC boost (no prior authorization required)
81267*	Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
81268*	Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (e.g., CD3, CD33), each cell type
81370*	HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, -C, - DRB1/3/4/5, and -DQB1
81371*	HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, and - DRB1 (e.g., verification typing)
81372*	HLA Class I typing, low resolution (e.g., antigen equivalents); complete (i.e., HLA-A, - B, and -C)
81373*	HLA Class I typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-A, - B, or -C), each
81374*	HLA Class I typing, low resolution (e.g., antigen equivalents); one antigen equivalent (e.g., B*27), each
81375*	HLA Class II typing, low resolution (e.g., antigen equivalents); HLA-DRB1/3/4/5 and - DQB1
81376*	HLA Class II typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81377*	HLA Class II typing, low resolution (e.g., antigen equivalents); one antigen equivalent, each
81378*	HLA Class I and II typing, high resolution (i.e., alleles or allele groups), HLA-A, -B, -C, and -DRB1
81379*	HLA Class I typing, high resolution (i.e., alleles or allele groups); complete (i.e., HLA-A, -B, and -C)
81380*	HLA Class I typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-A, -B, or -C), each
81381*	HLA Class I typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., B*57:01P), each
81382*	HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81383*	HLA Class II typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., HLA-DQB1*06:02P), each
86367*	Stem cells (i.e., CD34), total count
86812*	HLA typing; A, B, or C (e.g., A10, B7, B27), single antigen
86813*	HLA typing; A, B, or C, multiple antigens
86816*	HLA typing; DR/DQ, single antigen

86817*	HLA typing; DR/DQ, multiple antigens
86821*	HLA typing; lymphocyte culture, mixed (MLC)
86825*	Human leukocyte antigen (HLA) crossmatch, non-cytotoxic (e.g., using flow cytometry); first serum sample or dilution
86826*	Human leukocyte antigen (HLA) crossmatch, non-cytotoxic (e.g., using flow cytometry); each additional serum sample or sample dilution (List separately in addition to primary procedure)
86920*	Compatibility test each unit; immediate spin technique
86921*	Compatibility test each unit; incubation technique
86922*	Compatibility test each unit; antiglobulin technique
86923*	Compatibility test each unit; electronic
88240*	Cryopreservation, freezing and storage of cells, each cell line
88241*	Thawing and expansion of frozen cells, each
96401 – 96549*	Chemotherapy (no prior authorization required)
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic

Not Medically Necessary

0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, 1 leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, 1 leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, 1 leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell
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

VII. MEDICAL NECESSITY REVIEW

Prior authorization for certain drugs, devices, services and procedures may or may not be required. In cases where prior authorization is required, providers will submit a request demonstrating that a drug, service or procedure is medically necessary. For more information, refer to the Priority Health Provider Manual.

To access Evicore guidelines: Log into Priority Health Prism → Authorizations → Authorization Criteria Lookup.

To access InterQual guidelines: Log into Priority Health Prism → Authorizations → Authorization Criteria Lookup.

To access TurningPoint guidelines: Log into Priority Health Prism → Authorizations → Authorization Criteria Lookup.

To access EviCore, InterQual, or TurningPoint guidelines: Log into Priority Health Prism → Authorizations → Authorization Criteria Lookup.

Individual case review may allow coverage for care or treatment that is investigational yet promising for the conditions described. Requests for individual consideration require prior plan approval. All determinations of coverage for experimental, investigational, or unproven treatment will be made by a Priority Health medical director or clinical pharmacist. The exclusion of coverage for experimental, investigational, or unproven treatment may be reviewed for exception if the condition is either a terminal illness, or a chronic, life threatening, severely disabling disease that is causing serious clinical deterioration.

VIII. APPLICATION TO PRODUCTS

Coverage is subject to the member's specific benefits. Group-specific policy will supersede this policy when applicable.

- **HMO/EPO**: This policy applies to insured HMO/EPO plans.
- **POS**: This policy applies to insured POS plans.
- **PPO**: This policy applies to insured PPO plans. Consult individual plan documents as state mandated benefits may apply. If there is a conflict between this policy and a plan document, the provisions of the plan document will govern.
- **ASO**: For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern.
- **INDIVIDUAL**: For individual policies, consult the individual insurance policy. If there is a conflict between this medical policy and the individual insurance policy document, the provisions of the individual insurance policy will govern.
- **MEDICARE**: Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, this policy applies.
- **MEDICAID/HEALTHY MICHIGAN PLAN**: For Medicaid/Healthy Michigan Plan members, this policy will apply. Coverage is based on medical necessity criteria being met and the appropriate code(s) from the coding section of this policy being included on the Michigan Medicaid Fee Schedule. If there is a discrepancy between this policy and the Michigan Medicaid Provider Manual, the Michigan Medicaid Provider Manual will govern. If there is a discrepancy or lack of guidance in the Michigan Medicaid Provider Manual, the Priority Health contract with Michigan Medicaid will govern. For Medical Supplies/DME/Prosthetics and Orthotics, please refer to the Michigan Medicaid Fee Schedule to verify coverage.

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SUMMARY OF CHANGES

Deletions:

- I.A.2.a. Removed exclusion for persistent or active substance or alcohol abuse
- Stem Cell Transplant for Autoimmune Diseases: removed lower age limit of 18 for autologous hematopoietic stem cell transplantation for the treatment of multiple sclerosis

Additions:

- Stem Cell Transplant for Multiple Myeloma, Amyloidosis or Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and skin changes (POEMS syndrome): added risk-adapted criteria for tandem therapy for multiple myeloma

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Past committee review dates: 01/1993, 07/1995, 12/1995, 12/1999, 12/2001, 12/2002, 11/2003, 11/2004, 10/2005, 10/2006, 6/2007, 06/2008, 06/2009, 06/2010,0 6/2011, 06/2012, 06/2013, 08/2014, 08/15, 08/16, 08/17, 08/2018, 08/2019, 08/2020, 11/2020, 11/2021, 11/2022, 11/2023, 05/2024, 05/2025, 05/2026

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