Medical Coverage Policy

Effective Date.....1/15/2025
Next Review Date.....1/15/2026
Coverage Policy Number..... 0535

Stem Cell Transplantation: Non-Cancer Disorders

Table of Contents

Related Coverage Resources

Betibeglogene Autotemcel
Cell-Based Therapy for Cardiac and Peripheral Arterial Disease
Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell (HPC) Boost
Stem Cell Transplantation: Blood Cancers
Stem Cell Transplantation: Solid Tumors
Transplantation Donor Charges
Umbilical Cord Blood Banking

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not

covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses hematopoietic stem cell transplantation (HSCT) for some non-cancerous disorders.

Coverage Policy

Coverage for hematopoietic stem cell transplantation (HSCT) varies across plans. Refer to the customer's benefit plan document for coverage details.

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
Aplastic Anemia and Other Marrow Failure Syndromes	**Allogeneic HSCT is considered medically necessary for the treatment of ANY of the following conditions:** • severe aplastic anemia • Fanconi anemia • Diamond-Blackfan anemia • Congenital Amegakaryocytic Thrombocytopenia (CAMT) • Dyskeratosis Congenita • Paroxysmal nocturnal hemoglobinuria (PNH) • Shwachman-Diamond Syndrome
Autoimmune Diseases (systemic sclerosis, (scleroderma)	**Autologous HSCT is considered medically necessary for the treatment of systemic sclerosis (scleroderma) when ALL of the following criteria are met**: • adult 18 to 69 years of age • diffuse cutaneous systemic sclerosis (scleroderma) for 5 years or less with either: ➢ Pulmonary involvement with active interstitial lung disease and both: ○ Consistent bronchoalveolar cell composition or ground-glass opacities on computed tomography of the chest ○ Either a forced vital capacity (FVC) or a diffusing capacity of the lung for carbon monoxide (DLco) of less than 70% of the predicted value. ➢ Renal involvement • Individual does not have ANY of the following: ➢ active gastric antral vascular ectasia ➢ a DLco of less than 40% of the predicted value ➢ an FVC of less than 45% of the predicted value

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
	➢ a left ventricular ejection fraction of less than 50% ➢ a creatinine clearance of less than 40 ml per minute ➢ pulmonary arterial hypertension, ➢ more than six months of previous treatment with cyclophosphamide **HSCT for the treatment of any other autoimmune disease including but not limited to the following is considered not medically necessary:** • 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 • thrombotic thrombocytopenia purpura • type I diabetes mellitus • ulcerative colitis
Inherited Metabolic Disorders	**Allogeneic HSCT is considered medically necessary for the treatment of ANY of the following inherited metabolic disorders:** • Alpha mannosidosis • Cerebral X-linked Adrenoleukodystrophy • Farber disease type 2/3 • Fucosidosis • Gaucher disease types I and 3 • Hunter syndrome (MPS-II) • Hurler syndrome (MPS-IH) • Infantile malignant osteopetrosis • Krabbe disease (globoid leukodystrophy [GLD]) • metachromatic leukodystrophy (MLD) • Maroteaux-Lamy syndrome (MPS-VI) • Sly syndrome (MPS VII) • Wolman disease • Niemann-Pick disease type B **HSCT for the treatment of ANY of the following inherited metabolic disorders is considered not medically necessary:** • Scheie syndrome (MPS-IS) • Niemann-Pick disease type A • Sanfilippo disease (MPS-III)

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
Multiple Sclerosis (MS)	**Autologous HSCT is considered medically necessary for the treatment of multiple sclerosis when ALL of the following criteria are met:** • adult 18 to 55 years of age • relapsing-remitting* (RR) or secondary progressive* (SP) multiple sclerosis • Expanded Disability Status Scale (EDSS) score between 2.0 and 6.0 • failed treatment with one or more disease-modifying therapy(ies) (DMT) • evidence of either (or any) of the following while being treated with DMT: ➢ 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 *Definitions: Relapsing-remitting Multiple Sclerosis (RRMS): A multiple sclerosis course characterized by relapses with stable neurological disability between episodes. Secondary Progressive Multiple Sclerosis (SPMS): a progressive course (steadily increasing objectively documented neurological disability independent of relapses) following an initial relapsing-remitting course. Relapse: A monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hour, with or without recovery, and in the absence of fever or infection.
Primary Immunodeficiency Disorders	**Allogeneic HSCT is considered medically necessary for the treatment of primary immunodeficiency disorders including (this list may not be all-inclusive):** • B-cell (antibody) deficiencies (e.g., combined variable immunodeficiency [CVID]) • Combined T-cell and B-cell (antibody) deficiencies (e.g., severe combined immunodeficiency [SCID], combined immunodeficiency [CID], Wiskott-Aldrich syndrome [WAS]) • T-cell deficiencies (e.g., DiGeorge syndrome) • Defective phagocytes (e.g., Chediak-Higashi syndrome, chronic granulomatous disease, leukocyte adhesion defect) • Complement deficiencies (e.g., C1q) • Defects in innate immunity (e.g., anhidrotic ectodermal hyperplasia [NEMO deficiency], X-linked lyphoproliferative syndrome)

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
	• Autoinflammatory disorders (e.g., deficiency of adenosine deaminase 2 [DADA2])
Sickle Cell Disease and Thalassemia Major	**Allogeneic HSCT is considered medically necessary for the treatment of a child or adult at increased risk of complications of sickle cell disease (SCD) or thalassemia major.** **Autologous HSCT for an adult with SCD or thalassemia major is considered not medically necessary.*** ***Note: Autologous HSCT mobilization followed by apheresis to obtain CD34+ cells for Zynteglo manufacturing is medically necessary when Zynteglo meets coverage criteria for treatment of beta thalassemia (see Drug and Biologic Coverage Policy IP0486 Betibeglogene Autotemcel).**
Polycythemia Vera	**HSCT is considered not medically necessary for the treatment of polycythemia vera (PV).**
Type 2 Diabetes Mellitus	**HSCT for the treatment of type 2 diabetes mellitus is considered not medically necessary.**

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Hematopoietic stem cell transplantation (HSCT), also called hematopoietic cell transplantation (HCT) or stem cell transplant, is a type of treatment for cancer (and a few other conditions as well). Bone marrow produces all of the different cells that make up the blood, such as red blood cells, white blood cells, and platelets. All of the cells of the immune system are also made in the bone marrow. All of these cells develop from a type of precursor cell found in the bone marrow, called a hematopoietic stem cell. Hematopoietic stem cells are found in the peripheral blood and the bone marrow; therefore, stem cells can be collected or harvested from either location.

Some of the most effective treatments for cancer, such as chemotherapy and radiation, are toxic to the bone marrow. In general, the higher the dose, the more toxic the effects on the bone marrow. After the treatment, a healthy supply of stem cells is reintroduced, or transplanted. The transplanted cells then reestablish the blood cell production process in the bone marrow. HSCT is a method of replacing immature blood-forming cells in the bone marrow that have been destroyed

by drugs, radiation or disease. It may be autologous (i.e., using a person's own stem cells) or allogeneic (i.e., using stem cells donated by someone else).

- Autologous transplant — In autologous transplantation, an individual's own hematopoietic stem cells are removed before the high dose chemotherapy or radiation is given, and they are then frozen for storage and later use. After chemotherapy or radiation is complete, the harvested cells are thawed and returned to the individual, like a transfusion.
- Allogeneic transplant — In allogeneic transplantation, the hematopoietic stem cells come from a donor, ideally a brother or sister with a similar genetic makeup. If an individual does not have a suitably matched sibling, an unrelated person with a similar genetic makeup may be used. Under some circumstances, a parent or child who is only half-matched can also be used; this is termed a haploidentical transplant. In other circumstances, umbilical cord blood may be used in an umbilical cord blood transplant.
- Myeloablative transplant — A myeloablative transplantation uses very high doses of chemotherapy or radiation prior to transplantation with autologous or allogeneic hematopoietic stem cells.
- Non-myeloablative transplant — A non-myeloablative transplantation, sometimes referred to as reduced intensity transplant, allows an individual to have less intensive chemotherapy before transplantation with allogeneic hematopoietic stem cells. The idea is to minimize up front toxicity by using lower doses of intensive therapy, while retaining the immune graft versus tumor effect. This approach may be recommended for a variety of reasons including age, type of disease, other medical issues, or prior therapies.

Professional Societies/Organizations
Many factors affect the outcome of a tissue transplantation; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications for HSCT include (but are not limited to):

- poor cardiac function (ejection fraction less than 35%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal), unless related to disease
- poor renal function (creatinine clearance less than 50 mL/min) (not applicable for most autologous transplants)
- poor pulmonary function (diffusion capacity less than 50% of predicted)
- human immunodeficiency virus (HIV) if not controlled or active hepatitis B, hepatitis C or human T-cell lymphotrophic virus type 1 (HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

The American Society for Transplantation and Cellular Therapy (ASTCT) (formerly known as the American Society for Blood and Marrow Transplantation [ASBMT]) Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy (Kanate, et al., 2020).

Children (<18 years) (CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)	Allogeneic HCT	Autologous HCT
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi's anemia	R	N
Other bone marrow failure syndrome	R	N
Sickle cell disease	C	N

Children (<18 years) (CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)	Allogeneic HCT	Autologous HCT
Thalassemia	S	N
Congenital amegakaryocytic thrombocytopenia	R	N
Severe combined immunodeficiency (SCID)	R	N
T cell immunodeficiency, SCID variants	R	N
Wiskott-Aldrich syndrome	R	N
Hemophagocytic disorders	S	N
Severe congenital neutropenia	R	N
Chronic granulomatous disease	R	N
Other phagocytic cell disorders	R	N
IPEX syndrome	R	N
Juvenile rheumatoid arthritis	D	R
Systemic sclerosis	D	R
Other autoimmune and immune dysregulation disorders	R	N
Mucopolysaccharoidosis I (severe, Hurler syndrome)	R	N
Other mucopolysaccharoidoses (II, IV, VI)	D	N
Other lysomal metabolic diseases	D	N
Osteopetrosis (severe, recessive)	R	N
Osteopetrosis (intermediate)	D	N
Globoid cell leukodystrophy (Krabbe)	R	N
Metachromatic leukodystrophy	R	N
Cerebral X-linked Adrenoleukodystrophy	R	N

Adults (CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)	Allogeneic HCT	Autologous HCT
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi's anemia	R	N
Dyskeratosis congenita	R	N
Sickle cell disease	S	N
Thalassemia	D	N
Hemophagocytic syndromes, refractory	S	N
Common variable immunodeficiency	R	N
Wiskott-Aldrich syndrome	C	N
Chronic granulomatous disease	R	N
Multiple sclerosis	N	C
Systemic sclerosis	N	S
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn's disease	N	D
Polymyositis-dermatomyositis	N	D
Osteopetrosis (intermediate)	D	N
Cerebral X-linked adrenoleukodystrophy	R	N

The American Society for Blood and Marrow Transplantation (ASBMT) published a Position Statement on Autologous Hematopoietic Cell Transplantation for Treatment- Refractory Relapsing Multiple Sclerosis (MS) (Cohen, et al., 2019). The ASBMT Task Force recommends revising the

recommended indication for autologous hematopoietic stem cell transplantation (aHSCT or AHCT) in MS to "standard of care, clinical evidence available" for patients with relapsing forms of relapsing-remitting (RR) MS (RRMS or progressive MS 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 disease-modifying therapy (DMT), especially if disease activity continues despite treatment with high-efficacy DMTs and/or worsening disability. This revision of previous "developmental" guideline is based on the evidence from retrospective studies, clinical trials and meta-analyses/ systematic reviews.

- Patients most likely to benefit from aHSCT include those of relatively younger age with relatively short disease duration, a relapsing form of MS (RRMS or progressive MS with superimposed activity), accumulating disability but still ambulatory, and ongoing disease activity despite DMT.
- Patients with progressive MS without recent inflammatory disease activity (ie, clinical relapse or MRI lesion activity within the previous 1 to 2 years) are less likely to benefit.
- Some patients with other demographic or disease characteristics (eg, patients with early MS who have failed only a limited number of DMTs, but are considered at high risk for future disability, or some patients with progressive disease without recent activity) may benefit from aHSCT, but there is less supportive evidence for aHSCT in those populations.

The American Society for Blood and Marrow Transplantation (ASBMT) published a Position Statement on Systemic Sclerosis as an Indication for Autologous Hematopoietic Cell Transplantation (Sullivan, et al., 2018). Based on high-quality evidence, the ASBMT recommends systemic sclerosis be considered as "standard of care" indication for aHSCT.

Aplastic Anemia and Other Marrow Failure Syndromes: Aplastic anemia and other anemias are bone marrow failure syndromes. Bone marrow failure syndromes are a class of rare diseases with abnormal or absent hematopoeisis in one or more cell lines, and include acquired or congenital aplastic anemia, and other anemias. Most patients are diagnosed in childhood, mainly by presenting with hematologic findings such as single-cell or pancytopenia, myelodysplastic syndromes, or leukemia, particularly acute myeloid leukemia.

Acquired aplastic anemia is thought to have an autoimmune component in many patients, and immunosuppressive therapy is therefore a typical front-line therapy. Patients with aplastic anemia are classified based on the severity of their marrow aplasia. Allogeneic HSCT is considered a standard of care option for an individual with severe aplastic anemia (SAA). SAA requires at least two of the following:

- neutrophil count is less than 500 cells per microliter
- reticulocyte count is less than 20,000 per microliter
- platelet count is less than 20,000 per microliter

Inherited bone marrow failure syndromes are a heterogeneous group of rare hematological disorders characterized by the impairment of hematopoiesis, which harbor specific clinical presentations and pathogenic mechanisms. Some of these syndromes may progress through clonal evolution, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Most prominent are failures of DNA repair such as Fanconi Anemia and much rarer failure of ribosomal apparatus (e.g., Diamond Blackfan Anemia) or of telomere elongation such as Dyskeratosis Congenita (DC). In these congenital disorders, HSCT is often a consideration. However, HSCT will not correct the underlying disease and possible co-existing extra-medullary multi-organ defects, but will improve bone marrow failure (Fioredda, et al., 2018; Kojima and Ehlert, 2018; Dalle and Peffault de Latour, 2016).

Professional Societies/Organizations
Paroxysmal nocturnal hemoglobinuria (PNH) and Shwachman-Diamond Syndrome (SDS) are not addressed by *The American Society for Blood and Marrow Transplantation* (Majhail, et al., 2015). Brodsky (2014) states that allogeneic BMT following non-myeloablative conditioning regimens can cure PNH. Nelson and Myers (2018) note that hematopoietic stem cell transplant remains the only curative therapy for SDS individuals with severe aplastic anemia or malignant transformation.

Autoimmune Diseases: Autoimmune diseases are a very heterogeneic group of disorders with varying etiologies, levels of organ involvement and prognosis. Standard treatment for autoimmune diseases generally consists of immunosuppression, anti-inflammatory and/or anti-malarial medication, and supportive care. Dose escalation of immunosuppressive medication utilizing HSCT has been proposed for individuals who are refractory to standard treatment or have a disease considered to be life- or organ-threatening. Crohn's disease, juvenile idiopathic arthritis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and type 1 diabetes mellitus are some of the more common types of autoimmune diseases.

Literature Review
Systemic sclerosis (SSc): Evidence from three randomized trials (ASSIST [Burt, et al., 2011]; ASTIS [van Laar, et al., 2014]; SCOT [Sullivan, et al., 2018b]) demonstrates that autologous HSCT is more effective than conventional immunosuppressive therapies at inducing a better long-term survival, ameliorating skin thickening, and stabilizing internal organ function in severe systemic sclerosis. The patients who can likely benefit from autologous HSCT are those with rapid, progressive and diffuse skin involvement, persistent high levels of disease activity, and mild initial organ damage. A limited window of opportunity exists for HSCT treatment in SSc as severe irreversible organ involvement precludes transplantation. Autologous HSCT should be considered for carefully selected patients with early rapidly progressive diffuse SSc refractory to conventional therapy, and a poor prognosis for survival. Risks of HSCT include, but are not limited to, early treatment-related mortality, gonadal failure and secondary autoimmune diseases. Center experience and specialist expertise are further important factors for improving outcomes of autologous HSCT strategies (Shouval, et al., 2018; Walker, et al., 2018).

Crohn's disease (CD): A systematic review and meta-analysis was completed evaluating the efficacy and safety of autologous HSCT for refractory Crohn's disease (Qiu, et al., 2017). The authors concluded that autologous HSCT could be a complicated treatment with relatively high mortality and significantly high efficacy for refractory CD, which should be used with caution. However, more randomized control trials (RCTs) of larger samples using refined and standardized protocols and longer period of follow-up time are needed to further assess the outcomes of autologous HSCT therapy. A randomized clinical trial determined that for Crohn's patients (with impaired quality of life from refractory Crohn's disease not amenable to surgery despite treatment with three or more immunosuppressive or biologic agents and corticosteroids), HSCT, compared with conventional therapy, did not result in a statistically significant improvement in sustained disease remission at one year and was associated with significant toxicity (Hawkey, et al., 2015). Additional randomized controlled clinical trials are needed. At this time the role of HSCT has not been determined for this indication.

Diabetes Mellitus (DM): A meta-analysis on the safety and efficiency of different types of stem cell therapy for both type 1 and type 2 DM was completed (El-Badawy and El-Badri, 2016). The authors concluded the most promising therapeutic outcome was shown in mobilized marrow CD34+ stem cells; however, well-designed large scale randomized studies considering the stem cell type, cell number and infusion method in DM patients are needed. Although results are promising, there is insufficient evidence to establish the role of autologous or allogeneic HSCT for the treatment of type I diabetes mellitus. Professional society support in the form of published consensus guidelines is also lacking.

Juvenile Idiopathic Arthritis (JIA): There is limited data to determine the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for the treatment of juvenile idiopathic arthritis (JIA) (Silva, et al., 2018; Brinkman, et al., 2007). The role of HSCT for this indication has not yet been established.

Rheumatoid Arthritis (RA): Data are limited in the published peer-reviewed scientific literature. Park et al. (2018) conducted a phase IA feasibility trial with human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs). No short-term safety concerns were identified for the RA patients with moderate disease activity despite treatment with methotrexate. Small trials with uncontrolled study design limit the ability to determine safety and effectiveness of autologous or allogeneic HSCT for this indication. The role of HSCT in the treatment of RA has not yet been established.

Systemic Lupus Erythematosus (SLE): Lupus is a chronic (long-term) disease that causes systemic inflammation which affects multiple organs. Leone et al. (2017) conducted a systematic review of available evidence on HSCT therapy in patients with SLE and antiphospholipid syndrome (APS). The authors concluded that preliminary results of HSCT as a therapeutic option for SLE appear promising. However, the rate of adverse effects confines this option to very selected cases of SLE patients resistant or refractory to standard approaches. Further studies are warranted in order to assess the safety of the procedure for both the occurrence of secondary autoimmune disease and the rate of infection.

Professional Societies/Organizations
Systemic sclerosis (SSc): The European League against Rheumatism (EULAR) recommendations for the treatment of systemic sclerosis (SSc) (Kowal-Bielecka, et al., 2017) state HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance.

Hayes, Inc. published a Health Technology Assessment on Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Systemic Sclerosis (2019a) that concluded available evidence suggests that patients with rapidly progressive, poor-prognosis systemic sclerosis (SSc) could benefit from treatment with HSCT.

Hayes, Inc. published a Health Technology Assessment on Hematopoietic Stem Cell Transplantation For Treatment Of Multiple Sclerosis (2019b) noting that some evidence suggests patients experienced neurological improvement or stabilization. Also evidence suggests HSCT may confer benefits with respect to relapse and survival without signs of disease activity up to a median follow-up of approximately eight years.

Inherited Metabolic Disorders: Inherited metabolic disorders, also called inborn errors of metabolism or congenital metabolic disorders, are caused by genetic mutation, creating an enzyme deficiency that leads to an inability to breakdown metabolic waste products. The result is a progressive cellular accumulation of toxic substances, which damages organs, tissues, and the central nervous system. If left untreated, these disorders result in a progressive disease with neurological and psychomotor retardation, skeletal abnormalities, and life-threatening cardiac and pulmonary complications. Allogeneic HCT can arrest this progressive deterioration by introducing enzyme-producing cells that can cross the blood-brain barrier. There are several types of disorders, including:

- lysosomal storage diseases

- glycogen storage diseases
- disorders of carbohydrate metabolism
- disorders of amino acid metabolism
- organic acidemias
- disorders of fatty acid metabolism
- mitochondrial disorders

Literature Review
On behalf of the Agency for Healthcare Research and Quality (AHRQ), Ratko et al. (2012) conducted a systematic review of the literature to evaluate the benefits and harms of HSCT versus standard therapies or disease natural history in children with malignant solid tumors, inherited metabolic diseases, and autoimmune diseases. The authors noted that the evidence was insufficient for most pediatric indications. The overall grade of evidence strength was classified within the following four categories: high - further research is very unlikely to change confidence in the estimate of effect; moderate - further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate of effect; low - further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; and insufficient - any estimate of effect is very uncertain. Regarding the effect of HSCT compared to standard therapy, symptom management, or natural disease progression for metabolic disorders in children, AHRQ noted the following:

- Evidence suggesting a benefit of HSCT for overall survival:
  - Wolman's disease compared to disease natural history (high strength)
- Evidence suggested a benefit of HSCT for neuromuscular symptoms:
  - Farber's disease Type 2/3 compared to symptom management and disease natural history (high strength)
- Evidence suggesting a benefit of HSCT for neurocognitive symptoms:
  - Infantile ceroid lipofuscinosis compared to symptom management or disease natural history (low strength)
  - Attenuated form of MPS (mucopolysaccharidosis) II (Hunter's disease) compared to enzyme-replacement therapy (ERT) (low strength)
- Evidence suggesting a benefit of HSCT for neurodevelopmental symptoms:
  - Attenuated and severe forms of MPS II (Hunter's disease) compared to ERT (low strength)
- Evidence suggesting no benefit of single HSCT for overall survival:
  - Niemann-Pick Type A compared to symptom management (low strength)
- Evidence suggesting no benefit of HSCT for neurodevelopmental symptoms:
  - Gaucher Type III compared to ERT (low strength)
  - Juvenile form of GM1, juvenile Tay-Sachs compared to symptom management or disease natural history (both low strength)
  - MPS III (Sanfilippo) compared to symptom management, substrate reduction therapy, or disease natural history (low strength)
- Evidence suggesting no benefit of HSCT for neurocognitive symptoms:
  - Severe form of MPS II (Hunter's disease) compared to symptom management or disease natural history (low strength)
  - MPS III (Sanfilippo) compared to symptom management, substrate reduction therapy, or disease natural history (low strength)
  - Gaucher Type III compared to ERT (moderate strength)

Insufficient evidence to draw conclusions on the benefit or harm on overall survival with single allogeneic HSCT compared with symptom management and/or disease natural history for the following indications:

- Rapidly Progressive Diseases
  - mucolipidosis II (I-cell disease)
  - Gaucher disease type II
  - Cystinosis
  - infantile free sialic acid disease
- Slowly Progressive Diseases
  - Niemann-Pick type C
  - MPS IV (Morquio syndrome)
  - Aspartylglucosaminuria
  - Fabry's disease
  - β-mannosidosis
  - mucolipidosis III
  - mucolipidosis IV
  - glycogen storage disease type II (Pompe disease)
  - Salla disease
  - Adrenomyeloneuropathy
- Diseases With Both Rapidly and Slowly Progressive Forms
  - galactosialidosis (type unspecified)
  - Sandhoff disease (type unspecified)
  - Farber's disease type I
  - infantile GM1 gangliosidosis
  - juvenile GM1 gangliosidosis
  - infantile Tay-Sachs
  - juvenile Tay-Sachs
  - juvenile ceroid lipofuscinosis

Additional clinical studies investigating specific inherited metabolic disorders include, but are not limited to, the following:

Aspartylglycosaminuria is a very rare deficiency of the lysosomal enzyme. Aspartylglycosamidase causes the accumulation of a substance known as aspartylglucosamine in the body, resulting in disorders in the various body systems. The majority of cases are reported in Finland. Treatment of aspartylglycosaminuria is generally symptomatic and supportive.

Farber's Disease includes acid ceramidase deficiency and Farber's lipogranulomatosis. Type 1 is the more severe form which has central nervous system involvement. Patients with the milder form, Type 2/3 with either no or mild central nervous system symptoms, can live to their teenage years with chronic respiratory failure as the most common cause of death. Farber's disease is characterized by three classic symptoms: a hoarse voice or weak cry, small lumps of fat under the skin and in other tissues (lipogranulomas), and swollen and painful joints. Treatment for Farber's disease is symptomatic and supportive. Corticosteroid drugs may provide some relief for joint pain.

Fucosidosis may also be referred to as alpha-L-fucosidase deficiency. The treatment of fucosidosis is directed toward the specific symptoms that are apparent in each individual. Research in bone marrow transplant for fucosidosis and related lysosomal diseases is ongoing. Several case reports in the literature note that HSCT could reduce the severity and retard the progression of clinical neurological deterioration.

Gaucher disease is rare but is the most common type of lysosomal storage disorder. It is characterized by a deficiency of the enzyme glucocerebrosidase and results in the accumulation of harmful quantities of certain lipids, specifically the glycolipid glucocerebroside, throughout the body, especially within the bone marrow, spleen and liver. Researchers have identified three

distinct forms of Gaucher disease separated by the absence (type 1) or presence and extent (type 2 or type 3) of neurological complications.

- Gaucher disease type 1 is also known as non-neuronopathic, because it does not involve the central nervous system (brain and spinal cord).
- Gaucher disease type 2, also known as acute neuronopathic Gaucher disease, occurs in newborns and infants and is characterized by neurological complications due to the abnormal accumulation of glucocerebroside in the brain.
- Gaucher disease type 3, also known as chronic neuronopathic Gaucher disease, occurs during the first decade of life. In addition to blood and bone abnormalities, affected individuals develop neurological complications that develop and progress slower than in Gaucher disease type 2.

Treatment is individualized for each patient depending on the type of Gaucher disease. Type 1 Gaucher disease is considered treatable and mild, because it does not involve neurological symptoms since the brain is not affected. Type 2 is not considered to be treatable at this point due to the quick and irreversible brain damage in the infantile years. Type 3 still involves neurological damage, but these symptoms progress more slowly than in type 2. Enzyme replacement therapy (ERT) has proven effective for individuals with Gaucher disease type 1. ERT has not been effective in reducing or reversing certain neurological symptoms associated with Gaucher disease types 2 and 3. Other treatment is generally symptomatic and supportive.

Mucolipidoses (ML) are a group of inherited metabolic diseases in which abnormal amounts of carbohydrates and fatty materials (lipids) accumulate in cells. Damage to the cells occurs causing symptoms that range from mild learning disabilities to severe intellectual impairment and skeletal deformities. No cures or specific therapies for ML currently exist. Therapies are generally geared toward treating symptoms and providing supportive care to the child.

- Mucolipidosis I (Sialidosis) is characterized by a deficiency of the enzyme alpha-neuraminidase. There are two sub-types, type I and type II.
- Mucolipidosis II (I-cell disease or Inclusion-cell disease or ML II) is characterized by deficiencies of the enzymes neuraminidase and beta-galactosidase. The standard treatment of I-cell disease is symptomatic and supportive. Antibiotics are often prescribed for respiratory infections and yearly flu shots are important. Physical therapy is encouraged to maintain joint function and mobility as long as possible. Experimental therapies are aimed at treating I-cell disease as early as possible. Bone marrow replacement transplantation has been attempted for the treatment of this disorder, but the benefit was limited.
- Mucolipidosis III (Pseudo-Hurler polydystrophy) is characterized by the accumulation of certain complex carbohydrates (mucopolysaccharides) and fatty substances (mucolipids) in various tissues of the body. The symptoms of this disorder are less severe than those of I-cell disease.
- Mucolipidosis IV (ML IV) is caused by harmful alterations of a protein in the cell that is believed to be involved in the movement of molecules such as calcium across cell membranes.

Mucopolysaccharidoses (MPS disorders) are caused by the deficiency of one of ten specific lysosomal enzymes, resulting in an inability to metabolize complex carbohydrates (mucopolysaccharides) into simpler molecules. The accumulation of these large mucopolysaccharides in the cells of the body causes a number of physical symptoms and abnormalities. Bone marrow transplantation as a way to replace defective enzymes has been studied as a treatment for individuals with mucopolysaccharidosis. The effectiveness of BMT has varied greatly. Physical characteristics may improve, such as cloudy corneas may become clear, the size of an abnormally enlarged liver and spleen may decrease, and mucopolysaccharide levels

may drop. Skeletal malformations are unaffected. The effect on neurological symptoms varies considerably. Because BMT is a procedure that carries significant risks, it should only be considered in selected cases.

- MPS I (Hurler Disease, MPS Disorder I) has three subtypes of varying severity:
  - Scheie Syndrome (MPS IS) – milder form of MPS I
  - Hurler-Scheie Syndrome (MPS IH/S) – an intermediate form of MPS I
  - Hurler Syndrome (MPS IH) – the most severe form of MPS I

  Laronidase (Aldurazyme), an enzyme replacement therapy, is the first treatment FDA-approved specifically for Hurler syndrome. Other treatment is symptomatic and supportive.
- MPS II (Hunter syndrome) is caused by lack of the enzyme iduronate sulfatase. Previously, MPS II was classified as severe and attenuated based on severity. More recently, the terms slowly progressive and early progressive have been suggested. MPS II is now considered a continuous spectrum of disease. An enzyme replacement therapy, idursulfase (Elaprase), was approved as a treatment for MPS II. Other treatments of MPS II are symptomatic and supportive.
- MPS III (Sanfilippo disease or syndrome) includes four subtypes of MPS III: types A, B, C and D. Treatment of Sanfilippo syndrome is symptomatic and supportive. Clinical trials designed to gauge the safety and efficacy of several different approaches is under way. Therapeutic approaches include gene therapy, enzyme replacement therapy, substrate reduction therapy and stem cell therapy.
- MPS IV (Morquio syndrome) includes two forms:
  - Type A is caused by a defect in the GALNS gene. People with type A do not have an enzyme called N-acetylgalactosamine-6-sulfatase.
  - Type B is caused by a defect in the GLB1 gene. People with type B do not produce enough of an enzyme called beta-galactosidase.

  The body needs these enzymes to break down long strands of sugar molecules called keratan sulfate. In both types, abnormally large amounts of glycosaminoglycans build up in the body.
- MPS VI (Maroteaux-Lamy syndrome) occurs in three types: a classic severe type, an intermediate type, and a mild type. The syndrome is characterized by a deficiency in the enzyme arylsulfatase B (also called N- acetylgalactosamine-4-sulfatase), which leads to an excess of dermatan sulfate in the urine.
- MPS VII (Sly syndrome) is characterized by a deficiency of the lysosomal enzyme known as beta-glucuronidase.
- MPS IX is also known as hyaluronidase deficiency.

Niemann-Pick disease causes harmful quantities of lipids to accumulate in the brain, spleen, liver, lungs, and bone marrow. There is currently no cure for Niemann-Pick disease. Treatment is supportive. Restricting one's diet does not prevent the buildup of lipids in cells and tissues. The disorder may be best thought of as a spectrum of disease.

- At the severe end of the spectrum is a fatal neurodegenerative disorder that presents in infancy (Niemann-Pick disease type A).
- At the mild end of the spectrum, affected individuals have no or only minimal neurological symptoms, and survival into adulthood is common (Niemann-Pick disease type B). Type B, also called juvenile onset, usually occurs in the pre-teen years with symptoms that include ataxia and peripheral neuropathy. Treatment is aimed at addressing the symptoms present in each individual. Bone marrow transplantation has been attempted in a few individuals. Researchers are working to develop additional options for treatment, including enzyme replacement and gene therapy.
- Type C may appear early in life or develop in the teen or adult years. There are two types, NPC1 and NPC2. Affected individuals may have extensive brain damage that can cause an

inability to look up and down, difficulty in walking and swallowing, and progressive loss of vision and hearing. NPC1 is also called subacute juvenile form or chronic neuronopathic form.

Multiple Sclerosis (MS): Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disease of the central nervous system. MS is characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. There are no clinical findings that are unique to MS, but some are highly characteristic. The diagnosis of MS is relatively straightforward for patients who present with symptoms, characteristic MRI findings, and who have a relapsing-remitting course.

Literature Review

A recently published trial is the Multiple Sclerosis International Stem Cell Transplant (MIST) randomized clinical trial (Burt, et al., 2019). This trial compared the effect of nonmyeloablative HSCT versus disease-modifying therapy (DMT) on disease progression in patients with relapsing-remitting multiple sclerosis (RRMS). Inclusion criteria included: relapsing-remitting MS according to McDonald criteria; age 18 to 55 years; two or more clinical relapses, or one relapse and MRI gadolinium-enhancing lesion(s) at a separate time within the previous 12 months despite receiving treatment with disease-modifying therapy (DMT) (e.g., interferons, glatiramer acetate, fingolimod, natalizumab, or dimethyl fumarate); and an Expanded Disability Status Scale (EDSS) score between 2.0 and 6.0. Exclusion criteria included: primary or secondary progressive multiple sclerosis; hereditary neurologic diseases; pregnancy; pulmonary, cardiac, renal, or liver dysfunction; abnormal platelet or white blood cell counts; active infection; prior treatment with alemtuzumab or mitoxantrone; or use of natalizumab within the prior six months, fingolimod within three months, or, for teriflunomide (which undergoes extensive enterohepatic recycling), failure of oral cholestyramine to decrease teriflunomide to a plasma concentration of less than 0.02 µg/mL. Patients randomized to the DMT group received an FDA-approved DMT of higher efficacy or a different class than the therapy they were taking at the time of randomization, based on the judgment of their treating neurologist. In addition to DMT, patients in this group could receive immune-modulating or immunosuppressive drugs such as methylprednisolone, rituximab, intravenous immunoglobulin, or cyclophosphamide. After at least one year of treatment, patients in the DMT group who experienced progression of disability could cross over to receive HSCT. For patients randomized to the HSCT group, use of DMT was discontinued and variable washout periods were observed before admission for HSCT (six months for natalizumab, three months for fingolimod and dimethyl fumarate, and four months for rituximab). Patients who were receiving teriflunomide underwent either oral cholestyramine or activated charcoal clearance. Interferons and glatiramer acetate were continued until mobilization. After HSCT, patients did not receive immune-based therapies unless they experienced clinical relapse, new lesions on MRI, or both. Among 110 randomized patients, 103 remained in the trial, with 98 evaluated at one year and 23 evaluated yearly for five years (median follow-up, two years; mean, 2.8 years). Disease progression occurred in three 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 in the DMT group ($p < .001$). 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 ($p < .001$). There were no deaths and no patients who received HSCT developed nonhematopoietic grade four toxicities (such asmyocardial infarction, sepsis, or other disabling or potential life-threatening events).

The Autologous Haematopoietic Stem Cell Transplantation trial in MS (ASTIMS) is a multicenter, randomized, phase II study designed to assess the effect of aHSCT versus mitoxantrone (MTX) on the disease activity in MS, measured by MRI in the four years following treatment (Mancardi, et al., 2015). Inclusion criteria included: clinically defined MS; a secondary progressive (SP) or relapsing-remitting (RR) form that accumulates disability between relapses, with a documented

worsening during the last year (one step of EDSS, or 0.5 when EDSS is between 5.5 and 6.5), in spite of conventional therapy (interferon-b or glatiramer acetate or immunosuppressive therapy); and presence of one or more gadolinium (Gd)-enhancing areas on MRI. The EDSS score had to be between 3.5 and 6.5. A total of 21 patients were recruited from seven centers in two countries, Italy and Spain. All the patients had a follow-up of four years, and only two cases were followed for three years. Nine patients were randomized in the aHSCT and 12 in the MTX arm. Patients were randomized to receive intense immunosuppression (mobilization with cyclophosphamide and filgrastim, conditioning with carmustine, cytosinearabinoside, etoposide, melphalan, and anti-thymocyte globulin) followed by aHSCT or MTX 20 mg every month for six months. AHSCT significantly reduced the annualized relapse rate (ARR) as compared to MTX: ARR was 0.6 for the MTX arm and 0.19 for the aHSCT treatment group and the difference was statistically significant, despite the low power of the study for this endpoint ($p = 0.026$). Progression occurred at the end of follow-up in 48% of cases in the MTX arm and in 57% of the aHSCT-treated group. There was no statistical difference between the two groups ($p =0.50$). No difference in EDSS change at year one, two, three, and four was found between the treatment arms. This study is limited by small population size.

Hayes, Inc. published a Health Technology Assessment on Hematopoietic Stem Cell Transplantation For Treatment Of Multiple Sclerosis (2019b) noting that some evidence suggests patients experienced neurological improvement or stabilization. Also evidence suggests HSCT may confer benefits with respect to relapse and survival without signs of disease activity up to a median follow-up of approximately 8 years.

Two meta-analysis have recently been performed:

- Ge et al. (2019) evaluated 732 transplant patients from 18 trials and found:
  - The PFS was 75%, and the estimate of disease activity-free survival was 61% with 48-month follow-up. Subgroups analysis showed that low- and intermediate-intensity regimens were associated with higher PFS 80%.
  - Relapsing remitting MS (RRMS) benefited more from aHSCT than other MS subtypes with PFS 85%. Patients with Gd+ lesions at baseline MRI responded better to aHSCT with PFS 77%.
  - The estimate of TRM was 1.34%, and the overall mortality was 3.58%. TRM was significantly higher in high-intensity regimen studies (3.13%) and in older studies (1.93%) performed before 2006.
- Sormani et al. (2017) evaluated 764 transplant patients from 15 trials and found:
  - The pooled estimate of transplant-related mortality (TRM) was 2.1%. TRM was higher in older studies ($p=0.014$) and in studies with a lower proportion of patients with RRMS ($p=0.028$).
  - A higher baseline EDSS ($p=0.013$) was also significantly associated with a higher TRM.
  - Pooled rate of progression was 17.1% at two years and 23.3% at five years. Lower 2-year progression rate was significantly associated with higher proportions of patients with RRMS ($p=0.004$).
  - The pooled proportion of no evidence of disease activity (NEDA) patients at two years was 83% and at five years was 67%.

Other prospective and retrospective studies support the use of aHSCT in multiple sclerosis (Moore, et al., 2019; Muraro, et al., 2017; Nash, et al., 2017; Atkins, et al., 2016; Burt, et al., 2015; Shevchenko, et al., 2015).

Primary Immunodeficiency Disorders: When part of the immune system is either absent or not functioning properly, it can result in an immune deficiency disease. When the cause of this deficiency is hereditary or genetic, it is called a primary immunodeficiency disease (PIDD).

Researchers have identified more than 300 different kinds of PIDD. Primary immunodeficiency disorders, also known as congenital or inherited immunodeficiency disorders, are inherited disorders of immune system function, predisposing affected individuals to an increased rate and severity of infection and malignancy. Allogeneic hematopoietic cell transplantation (HCT) is the only potential cure for the severe forms of some of the immune deficiency diseases.

Primary immunodeficiency disorders are often classified according to the affected components of the immune system or immunologic phenotype. Although hundreds of primary immunodeficiency syndromes have been identified, less than 20 disorders account for over 90% of the known cases. Some of the more commonly occurring disorders include the following:

- B-cell (antibody) deficiencies
  - X-linked agammaglobulinemia
  - combined variable immunodeficiency (CVID)
  - hyper-IgM syndrome
  - selective IgA deficiency
- Combined T-cell and B-cell (antibody) deficiencies
  - severe combined immunodeficiency (SCID, bubble boy syndrome, Omenn syndrome, variant SCID)
  - partial combined immunodeficiency (CID)
  - Wiskott-Aldrich syndrome (WAS)
- T-Cell deficiencies
  - DiGeorge syndrome
- Defective phagocytes
  - Chediak-Higashi syndrome
  - chronic granulomatous disease
  - leukocyte adhesion defect
- Complement deficiencies
  - hereditary angioedema
- Deficiencies/cause unknown
  - hyper-IgE syndrome
  - chronic mucocutaneous candidiasis
- Defects in innate immunity
  - anhidrotic ectodermal hyperplasia (NEMO deficiency)
  - X-linked IgM syndrome
  - X-linked lymphoproliferative syndrome (XLP, Duncan Disease, Epstein-Barr Virus Susceptibility)
- Autoinflammatory disorders
  - tumor necrosis factor (TNF) receptor periodic fever
  - hyper-IgD syndrome

The American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology 'Practice parameter for the diagnosis and management of primary immunodeficiency' (Bonilla, et al., 2015) lists hematopoietic stem cell therapy as a possible therapeutic option for several immunodeficiency disorder categories and diagnoses. Here are some examples:

- Combined immunodeficiencies (CIDs)
- Immunodeficiency syndromes (Wiskott-Aldrich syndrome)
- Immune dysregulation (familial hemophagocytic lymphohistiocytosis [FHL]; autoimmune lymphoproliferative syndrome [ALPS]; immunodeficiency, polyendocrinopathy, X-linked [IPEX])

- Phagocytic cell defects (neutropenia, chronic granulomatous disease [CGD]; leukocyte adhesion deficiency [LAD]; mendelian susceptibility to mycobacterial disease [MSMD])
- Innate immune defects: (nuclear factor kB essential modulator [NEMO] deficiency, other NF-kB defects; warts, hypogammaglobulinemia, immunodeficiency, myelokathexis [WHIM] syndrome)

Sickle Cell Disease (SCD) and Thalassemia Major: SCD is a group of disorders that affects hemoglobin. People with this disorder have sickle or crescent-shaped red blood cells. SCD encompasses many sickling syndromes caused by abnormal sickle hemoglobin. The most common are sickle cell anemia (Hb SS), sickle-hemoglobin C disease (Hb SC), sickle-beta plus thalassemia, and sickle-beta zero thalassemia. The disease follows a variable clinical course which may include complications such as severe anemia, painful sickle cell crises, organ damage due to iron overload, acute chest syndrome, refractory pain, stroke, and premature death. Although supportive care, drug therapies, and red blood cell transfusions can ease symptoms and extend lifespan, allogeneic hematopoietic cell transplantation (HCT) is the only potential cure for SCD. Generally, clinical trials have included children and young adults up to 24 years in age. Individuals with SCD can decrease the chance of complications by staying as healthy as possible (e.g., up to date vaccinations). An individual is at increased risk of further complications based on their personal history of recurrent severe SCD complications.

Thalassemia major is a hereditary anemia resulting from defects in hemoglobin production. There are two types of thalassemia, alpha and beta, depending on which of the two hemoglobin chains is involved. Alpha and beta thalassemia have both mild (i.e., minor) and severe (i.e., major) forms. The severe form of this disease is known as beta thalassemia major, Cooley's anemia, thalassemia major or Mediterranean anemia. Although advances in supportive care and drug therapies have significantly improved the prognosis in beta thalassemia major, hematopoietic cell transplantation (HCT) remains the only treatment with a potential to cure this hemoglobinopathy.

Professional Societies/Organizations
A consensus document from the European Blood and Marrow Transplantation Inborn Error Working Party and the Paediatric Diseases Working Party provided consensus-based recommendations on indications for HSCT. Regarding children and adolescents with thalassemia major, the panel recommends young patients with an available HLA identical sibling should be offered HSCT as soon as possible before development of iron overload and iron-related tissue damage. Regarding adults, the panel recommends HSCT should be offered within controlled trials to adults who have been well-chelated since infancy. Regarding HSCT for SCD, the panel notes young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible, preferably at preschool age (Angelucci, et al., 2014).

Polycythemia Vera: Polycythemia vera (PV) is considered a myeloproliferative neoplasm. PV, also called polycythemia rubra vera, is a rare, acquired, chronic myeloproliferative neoplasm resulting from a mutation to a single hematopoietic stem cell in the marrow. Less common synonyms include splenomegalic polycythemia, Osler disease, polycythemia with chronic cyanosis, and myelopathic polycythemia. PV is characterized by an abnormal increase in the number of red and white blood cells as well as platelets, with red blood cell overproduction being predominant. The natural history of the disorder is characterized by a lifelong propensity for thrombotic complications and late-onset disease transformation into both myelofibrosis and acute myeloid leukemia.

Literature Review
There is insufficient evidence in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for PV. HSCT has been proposed as a potential treatment for PV; however, transplantation during the polycythemic phase of the disease is rarely appropriate. For

those patients in whom myeloid metaplasia with myelofibrosis develops or the disease evolves to acute myelogenous leukemia (AML), HSCT may be investigated as a possible treatment option at that time.

Professional Societies/Organizations
The National Comprehensive Cancer Network (NCCN®) Clinical Practice Guideline on Myeloproliferative Neoplasms, NCCN (v.2.2024, Aug 8, 2024) addresses polycythemia vera and does not discuss HSCT under treatment options (MS-31).

Type 2 Diabetes Mellitus: Type 2 DM is the most common form of diabetes. With this disorder the pancreas makes insulin, but doesn't use it efficiently and blood glucose levels rise higher than normal. Proponets are studying if HSCT can reduce exogenous insulin requirement while maintaining target HbA1c and an improvement in stimulated C-peptide response in patients with Type 2 DM. Several studies have been published. Study limitations include short-term follow-up only and small study population. In a systematic review, Hwang et al. (2019) suggests HSCT may be effective in improving the β cell function in Type 2 DM; "however, the observed effect should be interpreted with caution due to the significant heterogeneity and high risk of bias within the studies. Further verification through a rigorously designed study is warranted." There is insufficient evidence to demonstrate improved outcomes with HSCT for the treatment of type 2 DM. Further, there is a lack of professional society support in the form of published consensus guidelines. The role of HSCT has not been established for this indication.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Stem Cell Transplantation (Formerly 110.8.1) (110.23)	1/27/2016
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
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

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

References

1. Angelucci E, Matthes-Martin S, Baronciani D, Bernaudin F, Bonanomi S, EBMT Inborn Error and EBMT Paediatric Working Parties. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica. 2014 May;99(5):811-20.

2. Atkins HL, Bowman M, Allan D, Anstee G, Arnold DL, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet. 2016 Aug 6;388(10044):576-85.

3. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014 Oct 30;124(18):2804-11.

4. Burt RK, Balabanov R, Burman J, Sharrack B, Snowden JA, et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. JAMA. 2019 Jan 15;321(2):165-174.

5. Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. JAMA. 2015 Jan 20;313(3):275-84

6. Burt RK, Shah SJ, Dill K, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet 2011;378:498–506.

7. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Nov 5, 2024. Available at URL address: https://www.cms.gov/medicare-coverage-database/reports/local-coverage-proposed-lcds-alphabetical-report.aspx?proposedStatus=A&sortBy=title

8. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Nov 5, 2024. Available at URL address: https://www.cms.gov/medicare-coverage-database/reports/national-coverage-ncd-report.aspx?chapter=all&labOnly=allncd&sortBy=title

9. Cohen JA, Baldassari LE, Atkins HL, Bowen JD, Bredeson C, et al. Autologous Hematopoietic Cell Transplantation for Treatment-Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2019 May;25(5):845-854.

10. Dalle JH, Peffault de Latour R. Allogeneic hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. Int J Hematol. 2016 Apr;103(4):373-9.

11. El-Badawy A, El-Badri N. Clinical Efficacy of Stem Cell Therapy for Diabetes Mellitus: A Meta-Analysis. PLoS One. 2016 Apr 13;11(4):e0151938. eCollection 2016.

12. Fioredda F, Iacobelli S, Korthof ET, Knol C, van Biezen A, et al. Outcome of haematopoietic stem cell transplantation in dyskeratosis congenita. Br J Haematol. 2018 Oct;183(1):110-118.

13. Ge F, Lin H, Li Z, Chang T. Efficacy and safety of autologous hematopoietic stem-cell transplantation in multiple sclerosis: a systematic review and meta-analysis. Neurol Sci. 2019 Mar;40(3):479-487.

14. Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E, et al. Autologous Hematopoietic Stem Cell Transplantation for Refractory Crohn Disease: A Randomized Clinical Trial. JAMA. 2015 Dec 15;314(23):2524-34.

15. Hayes, Inc. Health Technology Assessment. Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Systemic Sclerosis. Hayes, Inc.; Jul 19, 2019a.

16. Hayes, Inc. Health Technology Assessment. Hematopoietic Stem Cell Transplantation For Treatment Of Multiple Sclerosis. Hayes, Inc.; Mar 18, 2019b.

17. Hwang G, Jeong H, Yang HK, Kim HS, Hong H, et al. Efficacies of Stem Cell Therapies for Functional Improvement of the β Cell in Patients with Diabetes: A Systematic Review of Controlled Clinical Trials. Int J Stem Cells. 2019 Jul 31;12(2):195-205.

18. Kanate AS, Majhail NS, Savani BN, Bredeson C, Champlin RE, Crawford S, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2020;26(7):1247-1256.

19. Kojima S, Ehlert K. Reconsidering the indication of haematopoietic stem cell transplantation for dyskeratosis congenita. Br J Haematol. 2018 Oct;183(1):11-12.

20. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, EUSTAR Coauthors, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017 Aug;76(8):1327-1339.

21. Leone A, Radin M, Almarzooqi AM, Al-Saleh J, Roccatello D, Sciascia S, et al. Autologous hematopoietic stem cell transplantation in Systemic Lupus Erythematosus and antiphospholipid syndrome: A systematic review. Autoimmun Rev. 2017 May;16(5):469-477.

22. Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015 Nov;21(11):1863-1869.

23. Mancardi GL, Sormani MP, Gualandi F, Saiz A; ASTIMS Haemato-Neurological Collaborative Group, On behalf of the Autoimmune Disease Working Party (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT); ASTIMS Haemato-Neurological Collaborative Group On behalf of the Autoimmune Disease Working Party ADWP of the European Group for Blood and Marrow Transplantation EBMT. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology. 2015 Mar 10;84(10):981-8.

24. Moore JJ, Massey JC, Ford CD, Khoo ML, Zaunders JJ, et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. J Neurol Neurosurg Psychiatry. 2019 May;90(5):514-521.

25. Muraro PA, Pasquini M, Atkins HL, Bowen JD, Farge D, Multiple Sclerosis–Autologous Hematopoietic Stem Cell Transplantation (MS-AHSCT) Long-term Outcomes Study Group, et al. Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. JAMA Neurol. 2017 Apr 1;74(4):459-469.

26. Nash RA, Hutton GJ, Racke MK, Popat U, Devine SM, et al. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. Neurology. 2017 Feb 28;88(9):842-852.

27. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Treatment by cancer type. Myeloproliferative neoplasms. v.2.2024 – Aug 8, 2024. Accessed Nov 5, 2024. Available at URL address: https://www.nccn.org/guidelines/category_1

28. Nelson AS, Myers KC. Diagnosis, Treatment, and Molecular Pathology of Shwachman-Diamond Syndrome. Hematol Oncol Clin North Am. 2018 Aug;32(4):687-700.

29. Park EH, Lim HS, Lee S, Roh K, Seo KW, et al. Intravenous Infusion of Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Rheumatoid Arthritis: A Phase Ia Clinical Trial. Stem Cells Transl Med. 2018 Sep;7(9):636-642.

30. Peffault de Latour R. Transplantation for bone marrow failure: current issues. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):90-98.

31. Qiu X, Feng JR, Chen LP, Liu S, Zhang M, Zhou Z, et al. Efficacy and safety of autologous hematopoietic stem cell therapy for refractory Crohn's disease: A systematic review and meta-analysis. Medicine (Baltimore). 2017 Jun;96(26):e7381.

32. Ratko TA, Belinson SE, Brown HM, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population. Rockville (MD): Agency for Healthcare Research and Quality (US); February 2012.

33. Shevchenko JL, Kuznetsov AN, Ionova TI, Melnichenko VY, Fedorenko DA, et al. Long-term outcomes of autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis: physician's and patient's perspectives. Ann Hematol. 2015 Jul;94(7):1149-57.

34. Shouval R, Furie N, Raanani P, Nagler A, Gafter-Gvili A. Autologous Hematopoietic Stem Cell Transplantation for Systemic Sclerosis: A Systematic Review and Meta-Analysis. Biol Blood Marrow Transplant. 2018 May;24(5):937-944.

35. Silva JMF, Ladomenou F, Carpenter B, Chandra S, Sedlacek P, et al. Allogeneic hematopoietic stem cell transplantation for severe, refractory juvenile idiopathic arthritis. Blood Adv. 2018 Apr 10;2(7):777-786.

36. Sormani MP, Muraro PA, Schiavetti I, Signori A, Laroni A,et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis. Neurology. 2017 May 30;88(22):2115-2122. Erratum in: Neurology. 2017 Jul 11;89(2):215.

37. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, SCOT Study Investigators. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. N Engl J Med. 2018b Jan 4;378(1):35-47.

38. Sullivan KM, Majhail NS, Bredeson C, Carpenter PA, Chatterjee S, et al. Systemic Sclerosis as an Indication for Autologous Hematopoietic Cell Transplantation: Position Statement from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2018 Oct;24(10):1961-1964.

39. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, EBMT/EULAR Scleroderma Study Group, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA. 2014 Jun 25;311(24):2490-8.

40. Walker UA, Saketkoo LA, Distler O. Haematopoietic stem cell transplantation in systemic sclerosis. RMD Open. 2018 Jun 17;4(1):e000533. eCollection 2018.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	Revised the policy statement for Sickle Cell Disease and Thalassemia Major.	1/15/2025
Annual Review	Revised the policy statement for sickle cell disease by removing the word "young" from the adult criteria.	2/15/2024