Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Aplastic Anemias

Policy # 00055
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Autoimmune Diseases is addressed separately in medical policy 00050.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a *repeat allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation* due to primary graft failure or failure to engraft to be **eligible for coverage.****

Based on review of available data, the Company may consider *autologous hematopoietic stem cell mobilization and pheresis* for the treatment of a genetic disease as part of the development of an FDA-approved ex vivo gene therapy (for example, betibeglogene autotemcel or elivaldogene autotemcel) to be **eligible for coverage.****

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider a*llogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation* for individuals with the following disorders

to be **eligible for coverage.**** In addition, individuals with Aplastic Anemia, Sickle Cell Disease or Thalassemia should meet the Disease Specific Criteria in the Policy Guidelines.

Patient Selection Criteria

Coverage eligibility may be considered for a*llogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation* for individuals with the following disorders when **ANY** of the following criteria are met:

- Bone Marrow Failure Syndromes
  - Acquired aplastic anemia (drug, idiopathic, immune disorder, toxin or viral infection); **OR**
  - Heritable bone marrow syndromes:
    - Congenital amegakaryocytic thrombocytopenia (CAMT); **OR**
    - Diamond-Blackfan anemia (DBA); **OR**
    - Dyskeratosis congenita; **OR**
    - Fanconi's anemia (FA); **OR**
    - Schwachman-Diamond syndrome (SDS); **OR**
  - Paroxysmal nocturnal hemoglobinuria (PNH)

; **OR**

- Immunodeficiencies
  - Hemophagocytic Lymphohistiocytosis (HLH); **OR**
  - Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome; **OR**
  - Severe Combined Immunodeficiency (SCID); **OR**
  - Wiskott-Aldrich Syndrome (WAS); **OR**
  - X-linked lymphoproliferative syndrome; **OR**
  - Chediak-Higashi syndrome; **OR**
  - Primary granulocyte dysfunction; **OR**
  - Chronic granulomatous disease

; **OR**

- Storage disorders
  - Hurler Syndrome (MPS I); **OR**
  - Hunter Syndrome (MPS II); **OR**
  - Maroteaux-Lamy Syndrome (MPS VI); **OR**
  - SanFilippo's (MPS III); **OR**
  - Gaucher disease

; **OR**

- Leukodystrophies
  - Adrenoleukodystrophy (ALD); **OR**
  - Globoid Cell Leukodystrophy (GBL; Krabbe's disease); **OR**
  - Metachromatic Leukodystrophy (MLD)

; **OR**

- Hemoglobinopathies
  - Sickle Cell Disease; **OR**
  - Thalassemia (homozygous beta-thalassemia)

; **OR**

- Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease); **OR**
- Other autosomal recessive disorders
  - Leukocyte adhesion deficiencies; **OR**
  - Kostmann's syndrome (severe congenital neutropenia, infantile genetic agranulocytosis).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers a*llogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation* for the treatment of all genetic diseases not

listed above including, but not limited to cystic fibrosis, and all acquired anemias not specifically identified in the Policy Guidelines below to be **investigational.***

Based on review of available data, the Company considers a*utologous hematopoietic stem cell transplantation* for the treatment of all genetic diseases including, but not limited to cystic fibrosis, and all acquired anemias to be **investigational.***

Based on review of available data, the Company considers a *planned tandem allogeneic hematopoietic stem cell transplantation or autologous hematopoietic stem cell transplantation* for all genetic diseases and for all acquired anemias to be **investigational.***

Based on review of available data, the Company considers a *second or repeat allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplant* due to persistent, progressive or relapsed disease to be **investigational.***

Based on review of available data, the Company considers *hematopoietic stem cell harvesting for a future but unscheduled transplant* to be **investigational.***

Based on review of available data, the Company considers a*utologous hematopoietic stem cell mobilization and pheresis* for the treatment of a genetic disease when the eligible for coverage statement above is not met to be **investigational.***

Policy Guidelines

Disease Specific Criteria

Aplastic Anemia Criteria:

- One of the following:
  - 55 years of age or younger do not need to have failed immunosuppressive therapy
  - Older than 55 years of age, or non-HLA identical donor, have to have failed immunosuppressive therapy

Sickle Cell Criteria:

- Children less than 16 years of age with homozygous SS disease or S-B thalassemia and who have had at least one of the following complications:
  - Stroke or CNS hemorrhage
  - Clinical evidence of progressive neurologic deterioration, for example, abnormal cerebral MRI and arteriogram and impaired neuropsychiatric testing
  - Sickle cell lung disease, recurrent acute chest syndrome or a combination of both requiring hospitalization and exchange transfusions
  - Sickle cell nephropathy

Thalassemia Criteria:

- Thalassemia major only **and**
- Individuals less than or equal to 30 years of age **and**
- The presence of minimal or no portal fibrous or active hepatitis

Background/Overview

Over the years, there has been a growing body of literature describing the application of allogeneic hematopoietic blood cell transplantation to correct genetic disorders and aplastic anemias. For certain genetic diseases and aplastic anemia, allogeneic hematopoietic blood cell transplantation may provide a potential treatment option.

Aplastic anemia is a rare, non-contagious disease that occurs when the bone marrow is damaged and stops making a sufficient quantity of blood cells for the body's needs. Aplastic anemia may be acquired or inherited, with the most commonly occurring being the acquired type. Most often, inherited aplastic anemias are diagnosed in children and acquired aplastic anemias are more common in adults. Some research suggests that stem cell damage may occur because the individual's immune system is reacting against bone marrow, interfering with the ability to make blood cells. Hematopoietic stem cell lines are no longer being replaced and the remaining stem cells are working less effectively, so the levels of red cells, white cells and platelets begin to drop. If blood levels drop too low, a person can experience fatigue (low red cells), bleeding under the skin, in the mouth and from the nose, or heavy periods (low platelets), or an increase in the number and severity of infections (low white cells). Aplastic anemias may result in the production of abnormal cells that may be associated with certain types of cancers such as leukemia. Examples of types of inherited

aplastic anemias include Fanconi anemia, Diamond-Blackfan syndrome, and Shwachman-Diamond syndrome. In general, treatment for aplastic anemia may include immunosuppressants, blood product transfusions, anti-infectives and bone marrow or stem cell transplant (also known as hematopoietic blood cell transplant).

Genetic disorders may involve inborn errors of metabolism. In these disorders, a single gene defect leads to the absence of a key protein, which leads to the clinical phenotype of the disease. Allogeneic HSCT provides a means of replacing the missing protein, potentially improving the clinical phenotype. The most significant experience has been in the treatment of mucopolysaccharidoses I (Hurler Syndrome) and leukodystrophies, although case reports have described transplantation therapy for many other genetic disorders.

Beta Thalassemia
Beta-thalassemia is an inherited blood disorder that causes a reduction of normal hemoglobin and red blood cells in the blood, through mutations in the beta-globin subunit, leading to inadequate delivery of oxygen in the body. The diminished levels of red blood cells can lead to a number of health issues including dizziness, fatigue, weakness, bone abnormalities and other serious complications. Transfusion-dependent beta thalassemia, the most severe form of the condition, typically requires life-long red blood cell transfusions as the standard course of treatment. However, frequent transfusions can be associated with multiple health complications of their own, including, but not limited to iron overload cardiomyopathy and cirrhosis of the liver due to an excessive build-up of iron in the body.

Cerebral Adrenoleukodystrophy (CALD)
Adrenoleukodystrophy is a rare, metabolic, X-linked disorder caused by a mutation in the ABCD1 gene which results in the toxic buildup of very long-chain fatty acids (VLCFA) in the brain and spinal cord. Cerebral ALD (CALD) is the most severe and neurodegenerative form of this condition. The accumulation of VLCFA in the adrenal cortex and white matter of the brain and spinal cord results in the progressive destruction of myelin. Without myelin, these nerves can no longer relay information to and from the brain.

The use of gene replacement therapy has been proposed for the treatment of CALD. Elivaldogene autotemcel is an autologous hematopoietic stem cell-based gene therapy for individuals with CALD.

This type of treatment requires a pre-treatment procedure which includes mobilization and pheresis to collect CD34+ cells for genetic manipulation as well as myeloablative conditioning.

Sickle Cell Disease
Sickle cell disease is a rare group of inherited disorders involving atypical hemoglobin molecules that distort red blood cells into a sickled shape. Complications of the disease can include severe pain crises, multiple organ dysfunction, acute chest syndrome and stroke. Typical therapeutic interventions are preventive and supportive measures. However, allogeneic HSCT has also been used under specific circumstances to replace the defective cells to correct the disorder.

Hematopoietic Stem Cell transplant (HSCT)
HSCT is a process which includes mobilization, harvesting, and transplant of stem cells after the administration of high dose chemotherapy (HDC), radiotherapy or a combination of both. High-dose chemotherapy involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The rationale for HDC is that many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (e.g., opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

1. Autologous - Stem cells harvested from the individual's own bone marrow prior to the cytotoxic therapy
2. Allogeneic - Stem cells harvested from a histocompatible donor (Note: this document does not require a specific level of histocompatibility be present as part of the medical necessity evaluation)

Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy or hematopoietic growth factors, or both.

In addition, 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 versus host disease.

The most appropriate stem cell source for a particular individual depends upon his or her disease, treatment history, and the availability of a compatible donor. The most appropriate source of stem cells for each person must balance the risks of graft failure and reinfusion of malignant cells in autologous procedures, the risks of graft rejection, and graft versus host disease in allogeneic procedures.

While the intensity of the regimens used for conditioning in conventional HDC varies, collectively they have been termed "myeloablative." Several less intense conditioning regimens have been developed recently and rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells. These regimens, collectively termed "non-myeloablative", also vary in intensity with substantial overlap between the ranges for "myeloablative" and "non-myeloablative" regimens. Studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. This manifests as a stable mixed donor-host hematopoietic chimerism. Once chimerism has developed, a further infusion of donor leukocytes may be given to eradicate malignant cells by inducing a graft vs. tumor effect. Non-myeloablative allogeneic transplants also referred to as "mini-transplant" or "reduced intensity conditioning (RIC) transplant", are thought to be potentially as effective as conventional HDC followed by allogeneic stem cell transplantation, but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen. Consequently, for individuals with malignancies who are eligible for conventional HDC/ allogeneic stem cell transplantation, conditioning with milder, non-myeloablative regimens represents a technical modification of an established procedure.

Tandem high-dose or non-myeloablative chemotherapy with autologous stem cell support or allogeneic stem cell support is the planned administration of two cycles of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The hypothesis is that eradication of

residual tumor cells can be achieved using multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

Other Considerations
Hematopoietic stem cell transplant (HSCT) is an important therapeutic modality for many malignant and nonmalignant hematologic diseases and its applicability continues to expand as its use in established therapies is refined and new indications are identified. In addition, the number individuals who could benefit from HSCT has increased due to advancements, such as reduced intensity conditioning regimens, which have made HSCT safer (Majhail, 2015). However, the risks associated with transplant-associated morbidity and mortality remain significant. Most transplant centers utilize forums, boards or conferences where the treatment options of individual HSCT candidates are discussed (Majhail, 2015). Okamoto (2017) notes:

The medical decision-making process for a transplant procedure is complex which requires assessing several factors besides the underlying indication for transplantation. Those include patient/disease factors, and transplant factors such as planed conditioning/graft-versus-host disease (GVHD) prophylaxis and stem cell source. Patient factors include their overall health and comorbidities, prior therapies, and how patients responded to those therapies, age, and disease/disease risk.

There are a number of clinical assessment and prognostic tools which evaluate individuals based upon multiple factors. The earlier, simpler tools, such as the Charlson Comorbidity Index (CCI) were useful in predicting outcomes but lacked the sensitivity of subsequent tools such as the HCT-specific comorbidity index (HCT-CI) The HCT-CI score has been validated in multiple HSCT settings to independently predict non-relapse mortality (NRM) rates by weighting 17 relevant comorbidities. The HCT-CI was further enhanced by the incorporation of some laboratory biomarkers into an augmented version. While these tools provide valuable prognostic information, the decision to transplant is unique to each individual and needs to include a specific risk-benefit analysis in partnership with the individual's physicians and other caregivers.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical

practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Bone Marrow Failure Syndromes
Ades and colleagues (2004) reported on 133 subjects treated with matched related allogeneic bone marrow transplants for the treatment of aplastic anemia. The conditioning regimen included thoracoabdominal irradiation (TAI) and cyclophosphamide for 100 subjects, and cyclophosphamide and antithymocyte globulin (ATG) for 33 subjects. The long-term study had a median follow-up of 13.6 years. Survival estimates for 5, 10, and 15 years were 69% ± 4.0%, 64.5% ± 4.5% and 58.7% ± 5.2%, respectively. Four individuals did not achieve engraftment and were not included in the long-term outcome data analysis. A total of 52 (79%) subjects developed extensive graft versus host disease (GVHD). A total of 46 deaths after transplantation occurred primarily resulting from GVHD, infection and 1 individual died of cancer.

Results from a retrospective study of 154 individuals with aplastic anemia treated with matched unrelated bone marrow transplants were reported by Kojima (2002). The probability of overall survival at 5 years was 56%. Grade III chronic GVHD was 20% and grade IV GVHD was 30%. Factors of poor prognostic outcomes were transplantation 3 years after diagnosis, individuals older than 20 years, preconditioning regimen without ATG and human leukocyte antigen (HLA)-A or B mismatch by DNA testing.

Allogeneic hematopoietic stem cell transplantation (HSCT) may be an option under specific circumstances for Diamond-Blackfan anemia (DBA), Fanconi's anemia (FA), paroxysmal nocturnal hemoglobinuria, and Schwachman-Diamond syndrome (SDS). In a report from the DBA registry, 20 of 354 registered individuals underwent HSCT, and the 5-year survival rates were 87.5% when recipients received HLA-identical sibling grafts (Gluckman, 2008). Dufour and colleagues (2008) reported in a summary of allogeneic HSCT from matched related donors over 6 years in FA, totaling 103 individuals, that overall survival ranged from 83-88%, with transplant-related mortality ranging from 8%-18.5% and average chronic GVHD of 12%. Santarone and colleagues (2010) performed a retrospective study of 26 individuals with paroxysmal nocturnal hemoglobinuria and concluded that HSCT may lead to a long-term cure rate as high as 60% in a heterogeneous cohort of seriously ill individuals with paroxysmal nocturnal hemoglobinuria.

Genetic mutations affecting ribosome function are associated with SDS and DBA. Sakamoto and colleagues (2010) reported that treatment of SDS and DBA may include stem cell transplantation. SDS is a rare (13 cases per 1 million) autosomal recessive genetic disorder. This disorder has clinical features which include pancreatic dysfunction, skeletal abnormalities, and aplastic anemia. Individuals with SDS are also at increased risk for myelodysplastic syndrome and transformation to acute myelogenous leukemia. SDS has been treated with HSCT.

Burroughs and colleagues (2009) stated the following in regard to SDS:

> In older individuals with this disease, the main causes of death are hemorrhage and infections due to associated hematological abnormalities such as marrow aplasia, neutropenia, MDS, or acute leukemia. Supportive measures include transfusions, pancreatic enzymes, antibiotics and GCSF. The only definitive therapy for marrow failure, MDS or leukemia is hematopoietic stem cell transplants.

Cesaro and colleagues (2005) reported on 26 individuals with SDS from the European Group for Blood and Bone Marrow Transplantation registry given HSCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myelogenous leukemia (MDS-AML) (n=9); or another diagnosis (n=1). Various preparative regimens were used; most included either busulfan (54%) or total-body irradiation (23%) followed by an HLA-matched sibling (n=6), mismatched related (n=1), or unrelated graft (n=19). Graft failure occurred in 5 (19%), and the incidence of grade III to IV acute and chronic GVHD were 24% and 29%, respectively. With a median follow-up of 1.1 years, overall survival (OS) was 65%. Deaths were primarily caused by infections with or without GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that presence of MDS-AML or use of total-body irradiation–based conditioning regimens were factors associated with a poorer outcome.

DBA is a rare (7 cases per 1 million) autosomal dominant red cell aplasia presenting during the first year of life. It is characterized by absent or decreased erythroid precursors in the bone marrow and may be associated with other congenital anomalies. Sakamoto and colleagues (2010) reviewed treatment for SDS and DBA and reported that treatment for these bone marrow failure syndromes include stem cell transplantation.

Bizzetto and colleagues (2011) reported on a European multicenter, retrospective study based on the Eurocord Registry. From 1994 to 2008, 64 individuals with hereditary bone marrow failure

syndromes were transplanted from related (n=20) or unrelated donors (n=44). Diagnoses were DBA (21 subjects), congenital amegakaryocytic thrombocytopenia (16 subjects), dyskeratosis congenita (8 subjects), SDS (2 subjects), severe congenital neutropenia (16 subjects) and unclassified (1 subject). In those who received grafts from related donors, all subjects but 1 received an HLA-matched sibling transplant. The cumulative incidence of neutrophil recovery at 60 days was 95%. Two subjects had grade II-IV acute graft-versus-host disease (GVHD), while the 2-year cumulative incidence of chronic GVHD was 11%. The 3-year overall survival rate was 95%. In those who received grafts from unrelated donors, 86% had HLA-mismatched grafts and 3 received 2 umbilical cord blood units. The cumulative incidence of neutrophil recovery at day 60 in this group was 55%. The 100-day cumulative incidence of grade II-IV acute graft-versus-host disease was 24%, while the 2-year cumulative incidence of chronic GVHD was 53%. The 3-year overall survival rate was 61%. Better overall survival was associated with age younger than 5 years and 6.1×10^7/kg or more total nucleated cells infused. Study results indicated that for individuals with hereditary bone marrow failure syndromes, related umbilical cord blood transplantation was associated with improved outcomes.

In 2012, Samarasinghe and colleagues retrospectively analyzed outcomes of children with idiopathic severe aplastic anemia in the United Kingdom who were treated with either immunosuppressive therapy (IST) or matched unrelated donor (MUD) HSCT. The 6-month cumulative response rate following IST was 32.5% (n=43). The 5-year estimated failure-free survival (FFS) following IST was 13.3%. The 44 successive children who received a 10-antigen MUD HSCT had an estimated 5-year FFS of 95.01%. Forty of these children had failed IST previously. There were no cases of graft failure and median donor chimerism was 100%.

Congenital amegakaryocytic thrombocytopenia (CAMT) is an exceedingly rare inherited autosomal recessive disorder characterized by thrombocytopenia and an absence of megakaryocytes at birth. Allogeneic HSCT is the only curative therapy. The published literature demonstrating successful outcomes of allogeneic HSCT for this disorder consists mainly of single or small case reports (Frangoul, 2010; King, 2005; Muraoka, 2005; Rao, 2015; Woods, 2014; Steele, 2005; Yesilipek, 2000). Additionally, Mahadeo and colleagues (2015) reported on 5 consecutive children with CAMT who demonstrated durable engraftment and correction of hematological abnormalities after treatment with myeloablative umbilical cord transplant. At a median follow-up of 14 years, all subjects were alive with sustained donor cell engraftment.

Dyskeratosis congenita is a rare inherited disorder of bone marrow failure with few allogeneic HSCT outcomes published. Hematopoietic cell transplantation represents the only known cure for bone marrow failure in this condition; however, it can result in significant toxicities. Dietz and colleagues (2011) reported on 6 individuals with dyskeratosis congenita that underwent allogeneic HCT with a nonmyeloablative conditioning regimen. Graft sources included related stem cells (1), unrelated bone marrow (2) and unrelated double umbilical cord blood (3). Complete donor engraftment was achieved in 5 of the 6 subjects. At a median follow-up of 26.5 months, 4 persons remained alive, 3 of whom were recipients of unrelated grafts. The authors concluded that encouraging short-term survival can be achieved with HSCT in persons with dyskeratosis congenita using a preparative regimen designed to promote donor engraftment and minimize life-threatening disease-specific complications such as pulmonary fibrosis.

A retrospective study by Gadalla and colleagues (2013) described results of 34 individuals with dyskeratosis congenita who underwent allogeneic HSCT between 1981 and 2009. The median age at transplantation was 13 years (range, 2-35). Approximately 50% of the transplants were from related donors. A total of 30 individuals achieved neutrophil recovery with a cumulative incidence of 73% by day 28. The day-100 probability of platelet recovery was 72%. The day-100 probability of grade II to IV acute GVHD and the 3-year probability of chronic GVHD were 24% and 37%, respectively. The 10-year probability of survival was 30% with 14 individuals alive at last follow-up. Twenty of the 34 (59%) died, and 10 deaths occurred within 4 months from transplantation because of graft failure (n=6) or other transplantation-related complications. Another 10 deaths occurred after 4 months; 6 of them occurred more than 5 years after transplantation, and 4 of these were due to pulmonary failure. Transplantation regimen intensity and transplantations from mismatched related or unrelated donors were associated with early mortality. Late mortality was attributed mainly to pulmonary complications and probably related to the underlying disease.

Immunodeficiency Disorders

Allogeneic HSCT may provide correction of primary immunodeficiencies, a genetically heterogeneous group of diseases that affect distinct components of the immune system. Gennery and colleagues (2008) reported that results of HSCT for primary immunodeficiencies have improved incrementally over time, with survival and cure of 90% for some defined diseases.

A rare and lethal autoimmunity disorder, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is caused by mutations in the forkhead box P3 (FOXP3) gene. Successful

allogeneic HSCT for IPEX syndrome has been described in the published literature consisting of mainly single case reports (Baud, 2001; Bis, 2015; Dorsey, 2009). Additionally, in 2007, Rao and colleagues described successful allogeneic HSCT in 4 individuals with IPEX syndrome using a reduced-intensity conditioning regimen that resulted in stable donor engraftment, reconstitution of FOXP3+ T regulatory CD4+ cells, and improvement of gastrointestinal symptoms.

Storage Disorders
The mucopolysaccharidoses (MPS) form a group of inherited metabolic diseases caused by the absence or dysfunction of specific enzymes required to break down mucopolysaccharides, also called glycosaminoglycans. The glycosaminoglycans accumulate in most tissues and affect all body systems, including the central nervous system. Historically, allogeneic HSCT has been utilized, mostly as a treatment for Hurler syndrome (MPS I). However, a specialty consensus review supported the use of allogeneic HSCT for other MPS diseases.

Hurler syndrome (MPS-I) is a lysosomal storage disease caused by an enzyme deficiency characterized by progressive multisystem morbidity and early childhood death if not treated. Aldenhoven and colleagues (2015) performed a retrospective analysis on the long-term outcomes of 217 individuals with Hurler syndrome treated with allogeneic HSCT. Study participants were successfully engrafted with a median follow-up age of 9.2 years. After transplantation, the clinical course of each subject improved; however, residual disease burden remained present in most cases. The authors noted that age at transplantation was an important predictor for better outcomes and early diagnosis and timely transplantation were of utmost importance.

Hunter syndrome (MPS II) is a rare X-linked recessive disorder that has an incidence estimated at 1.3 boys per 100,000 births (Guffon, 2008). Hunter Syndrome is characterized by mutations in the gene coding for the enzyme iduronate-2-suphatase (I2S). Guffon (2008) reported long-term results 7 to 17 years after allogeneic hematopoietic stem cell transplant in a series of 8 individuals with varying severities of Hunter Syndrome. Seven of the 8 individuals were alive at the time of the last assessment. The only death was due to a non-transplant related cause. Two individuals with normal intelligence quotient (IQ) at the time of transplantation attained adulthood while maintaining normal IQ as well as social and scholastic development.

Leukodystrophies
Leukodystrophies have been defined as inherited metabolic disorders of myelin, resulting in progressive destruction of, or the failure to develop normal white matter (Berger, 2001). Orchard and colleagues (2010) reported that adrenoleukodystrophy is an X-linked disorder, and in approximately 40% of cases, a progressive, inflammatory condition develops in the central nervous system. Early in the course of the disease, allogeneic transplantation can arrest the disease process in cerebral adrenoleukodystrophy. Disease phenotype and the extent of disease at the time of transplantation are of fundamental importance in determining outcomes for globoid cell leukodystrophy (Krabbe's disease) and metachromatic leukodystrophy. Both diseases are similar in that they have a varied phenotype. Allogeneic HSCT is considered potentially beneficial for late onset juveniles and adults with metachromatic leukodystrophy in early stages of the disease (Batzios, 2012; Gieselmann, 2010). A small case series (de Hosson, 2011) indicates that allogeneic HSCT may stop progression of the disease in select individuals. Those with later onset globoid cell leukodystrophy in the early stages of the disease may also benefit from allogeneic HSCT (Orchard, 2010).

Cerebral adrenoleukodystrophy (CALD) is a rare and life-threatening hereditary neurological disorder. Early childhood cerebral forms of CALD (called cerebral adrenoleukodystrophy) represent approximately 35 percent of all phenotypes in the group of conditions referred to as ALD. Disease phenotype does not correlate with the type of mutation, and different phenotypes can be seen within the same family. The result of the faulty gene is toxic buildup of VLCFAs, predominantly in the adrenal glands, brain, and spinal cord leading to loss of myelin sheath in the nerves and degeneration of function in the adrenal glands and central and peripheral nervous systems. Due to the X-linked nature of the disease, males (X-chromosome hemizygotes) are predominantly affected. Early symptoms of CALD may not be easily detected and may include adrenal insufficiency or behavioral problems. As the disease progresses, more severe symptoms arise, including vision and hearing problems/loss, seizures, swallowing problems, loss of voluntary and involuntary motor function, followed by death. Decline in intellectual abilities is also common. The 5-year survival rate is approximately 50% if untreated.

Prior to the FDA approval of elivaldogene autotemcel, the only available disease-modifying treatment for CALD was HSCT, which involves the transfer of blood stem cells from a genetically matched donor. Such treatment has been reported to provide stabilization of neurologic symptoms but has serious potential complications such as GVHD and graft failure, and matched donors are

frequently unavailable. For individuals with CALD who undergo successful HSCT at an early stage of disease, five-year survival is greater than 90 percent. HSCT does not appear to affect the course of adrenal dysfunction in patients with ALD, so patients require ongoing monitoring for adrenal dysfunction, and treatment, if necessary. HSCT is not recommended in individuals without MRI evidence of cerebral involvement, given that approximately one-half of these individuals will remain free of cerebral disease. HCST is also not recommended in individuals with advanced disease given that available evidence suggests that HCST does not improve clinical outcomes in these individuals. Management of patients with advanced cerebral involvement is primarily supportive.

To address CALD, bluebird bio, Inc. (Somerville, MA) has developed a new gene replacement therapy product, elivaldogene autotemcel (Skysona®‡). This product is composed of genetically modified autologous CD34+ cells that have been altered to include the wild-type ABCD1 DNA. This product is custom manufactured for each recipient using their own hematopoietic stem cells, which are harvested after mobilization, (a period of treatment intended to increase the desired type of cells used in the process). Once the cells have been collected, the individual undergoes full myeloablative conditioning to eliminate their existing hematopoietic system with the intention of replacing it with the new modified cells. The modified cells are infused into the individual and are intended to engraft into the bone marrow and create new stem cells, some of those cells migrate to the nervous system and adrenal glands, where they are intended to produce functional ALDP to locally breakdown VLCFAs and stabilize the treated individual's condition. The result of this type of treatment is intended to be life-long, but robust long-term data are not available at this time. Individuals undergoing treatment with elivaldogene autotemcel require long-term, regular monitoring for treatment success and for the evaluation of potential adverse events. Like HCST, elivaldogene autotemcel does not treat or prevent adrenal insufficiency. For more information on gene replacement therapy for CALD, see MED.00142 Gene Therapy for Cerebral Adrenoleukodystrophy.

Hemoglobinopathies

Early reports of allogeneic HSCT for sickle cell disease (Walters, 1996; Walters, 2000) describe treatment results of 48 children, less than 16 years of age. Results from the two reports were similar with overall survival rates ranging from 91%-94% and event-free survival from 73%-84% with a median follow-up ranging from 23.9 months to 57.9 months post transplantation. Vermylen and colleagues (1997) described a European study of 50 individuals with sickle cell anemia who underwent transplantation of hematopoietic stem cells (bone marrow, 48; cord blood, 2). Two

individuals (17 and 23 years old) did not fulfill the age criteria (less than 16 years), but still underwent transplant. Overall survival and event free survival at 11 years were 93% and 82%, respectively.

Bernaudin and colleagues (2007) reported on the largest experience as of that time related to allogeneic HSCT for sickle cell disease. Between November 1988 and December 2004, 87 individuals (age range, 2 to 22 years), received donor allografts from siblings after a myeloablative conditioning regimen (CR). The only change in the CR during the study period was the introduction of ATG in March 1992. The rejection rate was 22.6% before the use of ATG but 3% thereafter. With a median follow-up of 6 years (range, 2.0 to 17.9 years), the overall and event-free survival rates were 93.1% and 86.1%, respectively. There were 6 transplant related deaths reported with the cause being graft versus host (GVHD) in 4 of these individuals. None of the cord blood transplant recipients developed GVHD. Since 2000, there have been no deaths and only 2 graft rejections among 44 individuals. The authors also reported that since January 2000, 5 individuals over 15 years of age have successfully received transplants.

Hsieh and colleagues (2009) conducted a phase 1-2 study aimed to determine the feasibility of non-myeloablative allogeneic HSCT for adults with severe sickle cell disease. Ten adults (age range, 16 to 45 years) with severe sickle cell disease underwent non-myeloablative transplantation with peripheral-blood stem cells which were obtained from HLA-matched siblings. From the 10 individuals transplanted, only 2 persons were age 40 or over, with the remaining 8 ranging from 16-27 years of age. All 10 individuals were alive and there were no cases of GVHD at a median follow-up of 30 months post transplantation. The authors reported that successful engraftment occurred in 9 of the 10 adults. Study limitations included a small sample size.

Oringanje and colleagues (2020) performed a Cochrane review examining whether stem cell transplantation improves survival and prevents symptoms and complications associated with sickle cell disease. No randomized controlled trials assessing the benefit or risk of HSCTs were found and as such, the authors could not make recommendations for or against the procedure. Despite the lack of randomized trials, case series and observational reports have demonstrated improved overall survival and event free survival rates for allogeneic HSCT in certain individuals with sickle cell disease.

Allogeneic HSCT has been available as a potentially curative treatment of beta thalassemia for several decades. This involves the transplantation of stem cells from the donor's bone marrow or peripheral blood cells, and essentially involves replacing defective genes with healthy genes from another individual. Allogeneic HSCT is most effective when it is performed early in the course of disease before individuals experience complications related to transfusions or iron overload, ideally before 14 years of age. Survival rates of 90% or higher for early allogeneic HSCT have been reported. The decision to pursue HSCT is influenced by the availability of a well-matched donor; while the presence of human leukocyte antigen [HLA]-identical sibling donor is considered optimal, registry data has found similar survival outcomes in individuals who received HLA-matched related and HLA-matched unrelated donor transplantation (Li, 2019). Recent experiences evaluating transplantation with haploidentical donors in TDT patients have reported promising outcomes (Sun, 2018). HCT outcomes from the European Group for Blood and Marrow Transplantation registry database on 1493 patients with beta thalassemia major transplanted after year 2000 found an overall survival for the whole cohort at two years of 88% (range 68 to 91%) (Baronciani, 2016). Potential complications of HSCT include graft rejection and GVHD (Srivastava, 2017).

Gene replacement therapy is another potential curative treatment for beta thalassemia. Betibeglogene autotemcel (Zynteglo, Bluebird Bio) gene therapy involves inserting a functional copy of the HBB gene into a patient's hematopoietic stem cells outside the body using a lentiviral vector and then transplanting the modified stem cells back into the patient's blood stream, with the aim that the functional HBB gene will result in normal beta-globin protein expression. Zynteglo is a one-time gene therapy product that is administered as a single dose. While Zynteglo gene replacement therapy is not an autologous HSCT, it does require patients to undergo hematopoietic stem cell (HSC) mobilization followed by pheresis to obtain CD34+ cells for Zynteglo manufacturing (as well as administration of full myeloablative conditioning before infusion of Zynteglo) (U.S. FDA, 2022).

The safety and effectiveness of Zynteglo were demonstrated in two multicenter clinical studies that included adult and pediatric subjects with beta thalassemia requiring regular transfusions. Effectiveness was established based on achieving transfusion independence, which is attained when the patient maintains a pre-determined level of hemoglobin without needing any red blood cell transfusions for at least 12 months. Of 41 participants receiving Zynteglo, 89% achieved transfusion independence (U.S. FDA, 2022).

The use of autologous stem cells in gene replacement therapy removes the need for a compatible stem cell donor which has limited the ability of individuals to receive allogeneic SCT.

Infantile Malignant Osteopetrosis
Driessen and colleagues (2003) retrospectively analyzed 122 children who had received an allogeneic HSCT for autosomal recessive osteopetrosis between 1980 and 2001. The actuarial probabilities of 5 years of disease free survival were 73% for recipients of a genotype HLA-identical HSCT (n=40), 43% for recipients of a phenotype HLA-identical or 1 HLA-antigen mismatch graft from a related donor (n=21), 40% for recipients of a graft from a matched unrelated donor (n=20) and 24% for those who received a graft from an HLA-haplotype-mismatch related donor (n=41). In the latter group, a trend towards improvement was achieved at the end of the study period (17% before 1994, 45% after 1994, P=0.11). Causes of death after transplant were graft failure and early transplant-related complications. Conservation of vision was better in children transplanted before the age of 3 months. Final height was related to height at the time of transplant and better preserved in children transplanted early. Most children attended regular school or education for the visually handicapped. The authors noted that, at present, allogeneic HSCT is the only curative treatment for this rare, usually fatal, congenital disease.

Other Autosomal Recessive Disorders
Other autosomal recessive disorders that have been treated with allogeneic HSCT are leukocyte adhesion deficiencies and Kostmann's syndrome (severe congenital neutropenia, infantile genetic agranulocytosis).

Etzioni (2007) reported that individuals with leukocyte adhesion deficiencies suffer from life threatening bacterial infections, and in its severe form, death usually occurs in early childhood unless allogeneic stem cell transplantation is performed. Carlsson and colleagues (2011) reported that allogeneic HSCT is the only curative treatment for severe congenital neutropenia.

Cystic Fibrosis
In 2004, Spencer and Jaffe hypothesized about the use of autologous umbilical cord hematopoietic stem cell transplant and gene therapy to treat cystic fibrosis. However, there have been no prospective randomized trials to assess the efficacy and safety to support the use of stem cell transplantation for this indication.

Poor Graft Function
Poor graft function or graft failure is one of the major causes of morbidity and mortality after HSCT. Poor graft function is defined as slow or incomplete recovery of blood cell counts following a stem cell transplant or decreasing blood counts after initially successful hematopoietic engraftment following a stem cell transplant. There are various options for the management of poor graft function. Stem cell "boost" is a non-standardized term that is used to describe an infusion of additional hematopoietic stem cells to an individual who has undergone recent HSCT and has poor graft function (Larocca, 2006). The infusion of additional hematopoietic stem cells is to mitigate either graft failure or rejection with or without immunosuppression. This process may include the collection of additional hematopoietic stem cells from a donor and infusion into the transplant recipient. Note that a "boost" is distinct from a repeat transplant and that there may be separate medical necessity criteria for a repeat transplant.

Other Considerations
In 2015, the American Society for Blood and Marrow Transplantation (Majhail and colleagues) issued guidelines on indications for autologous and allogeneic hematopoietic cell transplantation. Definitions used for classifying indications were: standard of care (S); standard of care, clinical evidence available (C); standard of care, rare indication (R); Developmental (D); and not generally recommended (N). Nonmalignant indications for hematopoietic cell transplantation in "pediatric patients" (generally age below 18 years of age) include the following classifications:

- Severe aplastic anemia, new diagnosis (S for allogeneic and N for autologous)
- Severe aplastic anemia, relapse/refractory (S for allogeneic and N for autologous)
- Fanconi's anemia (R for allogeneic and N for autologous)
- Dyskeratosis congenita (R for allogeneic and N for autologous)
- Blackfan-Diamond anemia (R for allogeneic and N for autologous)
- Sickle cell disease (C for allogeneic and N for autologous)
- Thalassemia (S for allogeneic and N for autologous)
- Congenital amegakaryocytic thrombocytopenia (R for allogeneic and N for autologous)
- Severe combined immune deficiency (R for allogeneic and N for autologous)
- T cell immunodeficiency, SCID variants (R for allogeneic and N for autologous)
- Wiskott-Aldrich syndrome (R for allogeneic and N for autologous)
- Hemophagocytic disorders (R for allogeneic and N for autologous)

- Lymphoproliferative disorders (R for allogeneic and N for autologous)
- Severe congenital neutropenia (R for allogeneic and N for autologous)
- Chronic granulomatous disease (R for allogeneic and N for autologous)
- Other phagocytic cell disorders (R for allogeneic and N for autologous)
- IPEX syndrome (R for allogeneic and N for autologous)
- Juvenile rheumatoid arthritis (D for allogeneic and R for autologous)
- Systemic sclerosis (D for allogeneic and R for autologous)
- Other autoimmune and immune dysregulation disorders (R for allogeneic and N for autologous)
- Mucopolysaccharoidoses (MPS-1 and MPS-V1) (R for allogeneic and N for autologous)
- Other metabolic diseases (R for allogeneic and N for autologous)
- Osteopetrosis (R for allogeneic and N for autologous)
- Globoid cell leukodystrophy (Krabbe) (R for allogeneic and N for autologous)
- Metachromatic leukodystrophy (R for allogeneic and N for autologous)
- Cerebral X-linked adrenoleukodystrophy (R for allogeneic and N for autologous)

Nonmalignant indications for hematopoietic cell transplantation in adults (generally age 18 years or greater) include the following classifications:

- Severe aplastic anemia, new diagnosis (S for allogeneic and N for autologous)
- Severe aplastic anemia, relapse/refractory (S for allogeneic and N for autologous)
- Fanconi's anemia (R for allogeneic and N for autologous)
- Dyskeratosis congenita (R for allogeneic and N for autologous)
- Sickle cell disease (C for allogeneic and N for autologous)
- Thalassemia (D for allogeneic and N for autologous)
- Hemophagocytic syndromes, refractory (R for allogeneic and N for autologous)
- Mast cell diseases (R for allogeneic and N for autologous)
- Common variable immunodeficiency (R for allogeneic and N for autologous)
- Wiskott-Aldrich syndrome (R for allogeneic and N for autologous)
- Chronic granulomatous disease (R for allogeneic and N for autologous)
- Multiple sclerosis (N for allogeneic and D for autologous)
- Systemic sclerosis (N for allogeneic and D for autologous)

- Rheumatoid arthritis (N for allogeneic and D for autologous)
- Systemic lupus erythematosus (N for allogeneic and D for autologous)
- Crohn's disease (N for allogeneic and D for autologous)
- Polymyositis-dermatomyositis (N for allogeneic and D for autologous)

Conclusion
At this time there is a lack of evidence in the peer-reviewed medical literature, in terms of long-term safety and efficacy, to support the use of HSCT, for the indications listed above as investigational and not medically necessary. Additional study demonstrating improved outcomes is needed.

Supplemental Information/Definitions

Aplastic anemia: Bone marrow is unable to make blood cells.

Chest syndrome: A sudden breathing problem in some individuals with sickle cell.

Conditioning: A preparative regimen of chemotherapy given as part of a bone marrow/peripheral blood stem cell transplant protocol; may be myeloablative, non-myeloablative or tandem.

Consolidation: Repetitive cycles of treatment during the immediate post-remission period; used especially for leukemia; also known as intensification therapy.
Cytotoxic: Destructive to cells.
Eastern Cooperative Oncology Group (ECOG) Performance Status: A scale used to determine the individual's level of functioning. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score; based on the following scale:

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

Ex vivo: Outside of the living body. Ex vivo gene therapy refers to the process of taking an organ, cells, or tissue from a living body for a treatment or procedure, and then returning to the living body.

Failure to engraft: When the hematopoietic stem cells infused during a stem cell transplant do not grow and function adequately in the bone marrow.

Gaucher disease: A rare disease where there is a deficiency of the enzyme glucocerebrosidase.

Gene replacement therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction.

Graft-versus-host disease (GVHD): The condition that results when the immune cells of a transplant (usually of bone marrow) react against the tissues of the person receiving the transplant.

HDC: High-dose chemotherapy.

HDC/AlloSCS: High-dose chemotherapy with allogeneic stem cell support.

HDC/AuSCS: High-dose chemotherapy with autologous stem cell support.

Hematopoietic stem cells: Cells that give rise to distinct daughter cells, one cell that replicates the stem cell and one cell that will further proliferate and differentiate into a mature blood cell; also called progenitor cells.

Immunodeficiency: An inability to produce a normal complement of antibodies or sensitized T-cells in response to specific antigens.

Induction chemotherapy: A use of chemotherapy as initial treatment before surgery or radiotherapy of a malignancy.

Infantile malignant osteopetrosis: A hereditary disorder characterized by extreme density, hardness and fragility of the bones with partial or complete obliteration of the marrow cavities.

Karnofsky Score: A measure of the individual's overall physical health, judged by their level of activity; the score uses the following scale:

100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes
0%	Death

Kostmann's syndrome: An inherited disorder, causing low white blood cell counts and infection, noted during infancy.

Lansky Score Performance Status: A measure of the individual's overall physical health, judged by their level of activity; the score uses the following scale:

100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Leukodystrophy: Any of several inherited diseases characterized by degeneration of the white matter of the brain.

Myelin: The protective sheath of the nerve cells in the brain that are in charge of thinking and muscle control.

Non-myeloablative chemotherapy: Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

Paroxysmal nocturnal hemoglobinuria (PNH): A rare disease characterized by aplastic anemia, thrombosis, and red urine in the morning due to a breakdown of red blood cells.

Pheresis: Any procedure in which blood is collected from a donor and a fluid or solid portion (for instance, plasma, leukocytes, platelets, or cells) is removed and the rest of the blood is returned to the donor; A procedure commonly used for collecting stem cells; also known as apheresis.

Primary graft failure: When the hematopoietic stem cells infused during a stem cell transplant do not grow and function in the bone marrow.

Refractory: Not readily yielding to treatment.

Relapse: The return of symptoms and signs of a disease after a period of improvement.

Remission: A complete (CR) or partial (PR) disappearance of the signs and symptoms of disease in response to treatment; the period during which a disease is under control; a remission, however, is not necessarily a cure.

Salvage chemotherapy: The use of chemotherapy in an individual with recurrence of a malignancy following initial treatment, in hope of a cure or prolongation of life.

Severe combined immunodeficiency (SCID): Disorders where both immune cells and special immune proteins needed to fight disease are missing.

Sickle cell disease: Inherited blood disease characterized by deformed red blood cells shaped like sickles.

Stem cell mobilization: A procedure in which an individual's stem cells are stimulated out of the bone marrow into the bloodstream for collection for future reinfusion.

Tandem: A planned administration of two cycles of high-dose or non-myeloablative chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells; also known as double transplant.

Thalassemia: A group of inherited anemias affecting the hemoglobin chain genes.

Wiskott-Aldrich syndrome: An inherited, usually fatal, childhood immunodeficiency disease.

X-linked lymphoproliferative syndrome: A rare genetic disease of males transmitted from the mother in which the person's white blood cells are unable to fight infections.

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Policy History

Original Effective Date: 01/28/2002
Current Effective Date: 09/01/2023

12/06/2000	Medical Policy Committee review
01/28/2002	Managed Care Advisory Council approval
06/24/2002	Format revision
03/31/2004	Medical Director review
04/20/2004	Medical Policy Committee review. Format revision. No substance change to policy.
04/26/2004	Managed Care Advisory Council approval
04/05/2005	Medical Director review
04/27/2005	Medical Policy Committee review. Format revisions. Policy unchanged.
05/23/2005	Managed Care Advisory Council approval
05/03/2006	Medical Director review
05/17/2006	Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2008	Medical Director review
04/16/2008	Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2009	Medical Director review
04/15/2009	Medical Policy Committee approval. Coverage eligibility unchanged
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. Entire policy redone.
04/07/2011	Medical Policy Committee approval
04/13/2011	Medical Policy Implementation Committee approval. No change to coverage.

04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding updated
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. “Stem” removed from title and Policy. HSCT changed to HCT in Policy and Policy Guidelines and text. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/03/2021	Medical Policy Committee review

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06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Indicated that Shwachman-Diamond and Diamond-Blackfan are both syndromes under the Bone Marrow Failure Syndromes section that are eligible for coverage.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Title changed from "Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemia" to "Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Aplastic Anemias". Revised the entire When Services Are Eligible for Coverage and When Services Are Investigational sections. Added a When Services May Be Eligible for Coverage section. Revised the entire Policy Guidelines and Background/Overview sections. Removed the FDA or Other Government Regulatory Approval section. Revised the entire Rationale/Source, Supplemental Information and References sections.

Next Scheduled Review Date: 06/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38242, 38243 Add codes effective 09/01/2023: 38206, 38232, 38241
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.