POLICY AND PROCEDURE MANUAL

Policy Title: Hematopoietic Cell Transplant for Primary Immunodeficiency Disorders	**Policy Number: F.30**
Primary Department: Medical Management **Affiliated Department(s): N/A**	**NCQA Standard: N/A** **URAC Standard: N/A**
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Applicable Lines of Business: ☐MeridianCare ☒MeridianHealth ☐MeridianComplete ☒MeridianChoice	
Applicable States: ☐All ☒MI ☒IL ☐OH ☐_____ ☐_____	
Applicable Programs: ☒All ☐Other _____	
Policy is to be published: Internally Only ☐ Internally & Externally ☒	

Definition:

Severe Combined Immunodeficiency (SCID)	A group of disorders with several genetic causes. Children with SCID lack virtually all immune protection from bacteria, viruses, and fungi.
Wiskott–Aldrich Syndrome	Wiskott–Aldrich syndrome is characterized by thrombocytopenia with small platelets, eczema and recurrent infections.
Familial Hemophagocytic Lymphohistiocytosis (HLH)	Familial HLH is characterized by episodes of fever, hepatosplenomegaly and cytopenia.
Chediak–Higashi Syndrome	Chediak–Higashi syndrome is characterized by oculocutaneous albinism, recurrent infections and the presence of giant granules in hematopoietic and other cells.
Severe Congenital Neutropenia	Severe congenital neutropenia is characterized by an absolute neutrophil count less than 0.2×10^9 per liter.
Chronic Granulomatous Disease	Chronic granulomatous disease is characterized by recurrent pyogenic infections in patients with normal neutrophil numbers. Patients present with deep tissue infections and sepsis due to catalase-positive organisms such as *Staphylococcus aureus* and *Aspergillus fumigatus*.
HIGM1= Hyper IgM Syndrome (CD40 Ligand Deficiency)	Individuals may have high or normal levels of immunoglobulin M (IgM) antibody. People with X-linked hyper IgM syndrome have low levels of three other classes of antibodies: immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin E (IgE).

Griscelli Syndrome Type 2	These individuals have immune system abnormalities in addition to having hypopigmented skin and hair.
X-linked Lymphoproliferative Disease	X-linked lymphoproliferative disease (XLP) is a disorder of the immune system and blood-forming cells that is found almost exclusively in males. These individuals experience an exaggerated immune response to the Epstein-Barr virus (EBV) which leads to hemophagocytic lymphohistiocytosis(HLH).
Leukocyte Adhesion Defect Type 1	This is an immunosystem malfunction where bacterial and fungal infections most commonly occur on the skin and mucous membranes such as the moist lining of the nose and mouth.

Policy:

Immunodeficiency causes persistent or recurrent infections, severe infections by organisms that are normally mild, incomplete recovery from illness or poor response to treatment, and an increased incidence of cancer and other tumors. Opportunistic infections are widespread infections by microorganisms that are usually controllable.

Immunodeficiency disorders may affect any part of the immune system. Most commonly, this involves decreased functioning of T or B lymphocytes (or both), or deficient antibody production. The causes include congenital (inherited) defects and acquired immunodeficiency caused by a disease that affects the immune system (US National Library of Medicine, 2007).

Primary immune deficiency diseases (PIDD) are due to genetic factors which cause people to be more susceptible to infections. There are more than 200 different forms of PIDDs. These diseases are classified by either adaptive immunity (i.e., T-cell, B-cell or combined immunodeficiencies) or of innate immunity (e.g., phagocyte and complement disorders). The treatment of PIDDs is complex and generally requires both supportive and definitive strategies. Immune globulin ~~g~~ replacement therapy is the mainstay of therapy for B-cell disorders, and is also an important supportive treatment for many patients with combined immunodeficiency disorders. The treatment of innate immunodeficiency disorders varies depending on the type of defect, but may involve antifungal and antibiotic prophylaxis, cytokine replacement, vaccinations and bone marrow transplantation.

Hematopoietic stem cell transplantation (HSCT) is the only potentially curative nonexperimental therapy available for many primary immunodeficiencies. It is important to utilize early transplantation before the development of serious infections that contribute to a significant increase in the risk of mortality following HSCT.

The long-term prognosis of HSCT for primary immunodeficiency has improved with advances in early diagnosis with newborn screening, high-resolution tissue typing, refinement and tailoring of preconditioning regimens (especially for T cell-negative, B cell-negative [T-B-] severe combined immunodeficiency [SCID]), use of reduced-intensity conditioning, depletion of donor lymphoid cells using biologics and CD34+ selection, supportive care, early detection and treatment of viral infections, and graft-versus-host disease (GVHD) management.

Human-leukocyte antigen (HLA) typing should be undertaken as soon as a diagnosis of severe combined immunodeficiency or other immunodeficiency potentially correctable by HSCT is established. The risks of HSCT are reduced in patients who have not yet developed infectious complications of immunodeficiency . Furthermore, the thymus microenvironment may deteriorate over time and be less capable of supporting T cell development. Although HSCT should be undertaken as early as possible in the patient's life, there are an increasing number of reports of successful transplant in young adults .

Procedure:

Criteria for Coverage:

Many factors affect the outcome of tissue transplantation; the selection process is designed to obtain the best result for each individual. Overall health, age, and disease stage are extremely important considerations in evaluating candidates.

As consideration for hematopoietic stem cell transplantation these guidelines **MUST** be met[26]:

1. Cardiac function evaluation:
    a. Left ventricular ejection fraction equal or greater than 40 %[26]
    b. If present, coronary artery disease and cardiac arrhythmias must me controlled/stable
2. Pulmonary function evaluation:
    a. Forced vital capacity (FVC)/forced expiratory volume in 1 second (FEV1)/diffusion capacity of the lung for carbon monoxide (DLCO) equal to or greater than 50 % predicted.
3. Renal function with a serum creatinine < 2 mg/dl of Cl_{cr} > 50 ml/min
4. Liver function studies indicate no frank cirrhosis.[26]
5. No active infection must be present including any of the following:

    a. Human immunodeficiency virus (HIV)
    b. Hepatitis B virus (HBV)
    c. Hepatitis C virus (HCV)
    d. Human T-cell lymphotropic virus (HTLV)-1

6. Dental exam, x-rays, and treatment completed to eliminate sources of infection in the oral cavity.
    a. Examples include, but are not limited to gum disease, tooth decay, tooth abscesses, and poor oral hygiene.
7. Karnofsky rating 70% or greater and/or Eastern Cooperative Oncology Group (ECOG) performance status less than 2
8. Documentation of member's ability to understand the risks of the procedures.
9. Emotional and psychiatric stability, including a strong family or alternative support network (documented by formal social work evaluation)
10. Absence of psychiatric disease that would interfere with the member's ability to comply with the pre- or post-transplant therapeutic regimen

The rationale to proceed with transplantation, if a transplant candidate has sub-optimal organ function or a per-existing comorbid conditions (s) must be documented within the candidate's medical record by the BMT physician.

Specific Diagnoses:

*Criteria for **Allogeneic** Hematopoietic Cell Transplantation:*

Meridian considers allogeneic hematopoietic cell transplantation medically necessary for members with the following inherited primary immunodeficiencies who will have a suitable human leukocyte antigen (HLA) matched donor:

- Defective T and B lymphocytes
    - Wiskott–Aldrich syndrome
    - X linked hyper IgM syndrome (CD4 IgM deficiency)(HIGMI1)
    - AID and UNG deficiencies (autosomal recessive hyper 1gM syndromes)
- CD40 deficiency (autosomal recessive hyper IgM syndromes)Dysfunctional T lymphocytes
    - Chediak-Higashi syndrome
    - Familial hemophagocytic lymphohistiocytosis (HLH) (defects in *perforin, MUNC,* etc.)
    - Griscelli syndrome type 2
    - DiGeorge syndrome
    - X-linked lymphoproliferative disease (XLP)
    - Autoimuune lymphoproliferative syndrome
    - Major Histocompatability Complex (MHC) class I deficiency
    - Major Histocompatability Complex (MHC) class II deficiency
- Absent T- and B-lymphocyte function
    - Severe combined immunodeficiency (multiple types) (SCID)
    - Common variable immune deficiency (CVID)
- Absent or defective neutrophil function

    - Kostmann syndrome also known as-Severe congenital neutropenia or autosomal recessive type 3 (SCN3)
    - Chronic granulomatous disease
    - Leukocyte adhesion defect Type 1
    - Severe congenital neutropenia
- Others:
    - WAS X-linked thrombocytopenia
    - Interferon gamma receptor defects
    - NF kappa B essential modifier (NEMO) deficiency
    - Interleukin-10 (IL-10) receptor deficiency
    - Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)
    - Cartilage hair hypoplasia

Absolute Contraindications:

Meridian considers *allogeneic hematopoietic cell transplantation* for the treatment of complement deficiency experimental and investigational because the effectiveness of this approach has not been established.

Criteria for Autologous Hematopoietic Cell Transplantation:

Meridian considers *autologous hematopoietic cell transplantation* experimental for the treatment of primary immunodeficiency disorders because its effectiveness has not been recognized. Although allogeneic HSCT is an accepted therapy for primary immunodeficiency disorders, defects in the affected individual's immune system preclude the use of autologous HSCT for this indication

Facilities performing stem cell transplants must be accredited by the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee and compliant with the FACT_JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration manual

Member Assessment of Compliance with Plan of Care (applicable for ages 10 and above):
There should also be no significant history of medical noncompliance:

1. Alcohol screen- abstinence for the past 6 months prior to actual transplant approval, if member history includes use of alcohol. If no history exists then 1 negative alcohol screen must be submitted for members with no history of past alcohol use
2. Drug screen-abstinence for the past 6 months prior to actual transplant approval if history exists of drug use. If no history exists then 1 negative drug screen must be submitted for members with no history of positive drug screen.
3. Nicotine screening- abstinence for the past 6 months prior to actual transplant approval if history of smoking. If no history exists then 1 negative cotinine level must be submitted

Refusal or failure to undergo monthly testing for those members with a history of alcohol, tobacco, and/or drug use will be interpreted as a positive test result.

Six month abstinence period may be shortened in cases where patient's condition is sufficiently advanced that mortality is reasonably expected before the full abstinence period can be completed. Patients granted a waiver of the six month abstinence period require documentation of participation in a formal outpatient treatment program, when practical, as well as serial blood or urine testing no less frequently than monthly. A positive test result at any time prior to the procurement phase will result in denial.

Appendix – KPS and ECOG: One tool that assesses a patient's performance status is the Karnofsky Performance Scale. The scale ranges from 0 to 100%, with 100% representing patients without evidence of disease and 0% being dead. A status score of 70% denotes those patients that are able to care for themselves but may not be able to effectively work, shop, drive, or care for family members; patients with an irreversible score or less the 70% generally have a poor prognosis.

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

The Eastern Cooperative Oncology Group (ECOG) developed a performance status tool. This tool assesses the patient's disease progression, the impact of the disease on daily living, and provides information used to determine proper treatment and prognosis. Patients are classified based on the following information:

0	Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5	Death

Line of Business Applicability:
This policy applies to Michigan Medicaid, Illinois Medicaid, and Individual plans.

For **Medicaid/Medicaid Expansion Plan** members, this policy will apply. Coverage is based on medical necessity criteria being met and the codes being submitted and considered for review being included on either the Michigan Medicaid Fee Schedule (located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_42542_42543_42546_42551-159815--,00.html), or the Illinois Medicaid Fee Schedule (located at: http://www.illinois.gov/hfs/MedicalProviders/MedicaidReimbursement/Pages/default.aspx). If there is a discrepancy between this policy and either the Michigan Medicaid Provider Manual (located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_5100-87572--,00.html), or the Illinois Medicaid Provider Manual (located at: http://www.illinois.gov/hfs/MedicalProviders/Handbooks/Pages/default.aspx)the applicable Medicaid Provider Manual will govern.

For **Individual** members, consult the individual insurance policy. If there is a discrepancy between this policy and the individual insurance policy document, the guidelines in the individual insurance policy will govern.

State specific special instructions:

None: ☒

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State Letters/Bulletins					
CMS National/Local Coverage Determination (NCD/LCD)	110.23 NCD for Stem Cell Transplantation				
Medicare Managed Care Manual:					
Medicaid CFR:					
State Administrative Codes:					
Contract Requirements:					
Related Policies:					