POLICY AND PROCEDURE MANUAL

Policy Title: Hematopoietic Cell Transplant for Aplastic Anemia and Bone Marrow Failure Syndromes	**Policy Number: F.29**
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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 ☒	

Definitions:

Aplastic anemia (AA)	characterized by pancytopenia due to the bone marrow's failure to produce blood cells. In most patients the etiology is unknown (idiopathic) or can be due to infections, drugs, or toxins as well as intrinsic defects of hematopoietic stem cells, defects in the marrow micro-environment, and abnormal humoral or cellular immune control of hematopoiesis and hereditary causes such as in Fanconi's anemia or Diamond-Blackfan syndrome.
Fanconi Anemia	The most frequently reported of the rare inherited bone marrow failure syndromes with approximately 2000 cases reported in the medical literature. Fanconi anemia has increased numbers of chromosome breaks; the breakage rate was found to be specifically increased by the addition of deoxyribonucleic acid (DNA) cross-linkers, such as diepoxybutane (DEB) or mitomycin C (MMC). This led to the identification of patients with Fanconi anemia and aplastic anemia without birth defects and the diagnosis of Fanconi anemia in patients without aplastic anemia but with abnormal physical findings. The advent of molecular diagnostics has further improved the specificity of Fanconi anemia diagnosis. Possible complications of Fanconi anemia include hemorrhages, infections, leukemia, myelodysplastic syndrome, liver tumors, and other cancers
Diamond–Blackfan Anemia (DBA)	Characterized by normocytic or macrocytic anemia (low red blood cell counts) with decreased erythroid progenitor cells in the bone marrow. This usually develops during the neonatal period. About 47% of affected individuals also have a variety of congenital abnormalities, including craniofacial malformations, thumb or upper limb abnormalities, cardiac defects, urogenital malformations, and cleft palate. Low birth weight and generalized growth delay are sometimes observed. DBA patients have a modest risk of developing leukemia and other malignancies

Paroxysmal Nocturnal Hemoglobinuria (PNH)	Characterized by the clinical triad of hemolytic anemia, thrombophilia, and cytopenia. This is caused by an acquired mutation of the PIG (phosphatidylinositol glycan)-A gene of the pluripotent hematopoetic stem cell. This results in a deficiency of GPI (glycosylphosphatidylinositol)-anchors and GPI-anchored proteins on the surface of affected blood cells. Treatment of PNH is mainly symptomatic. Allogeneic BMT is the only curative option in case of severe complications during the course of the diseases.
Acquired pure red cell Aplasia (PRCA)	A part of a unique form of AA, is a rare condition of profound anemia characterized by the absence of reticulocytes and the virtual absence of erythroid precursors in the bone marrow.

Policy: The bone marrow failure syndromes include a group of disorders than can be either inherited or acquired. These diseases are disorders of the hematopoietic stem cell that can involve either 1 cell line or all of the cell lines (erythroid for red cells, myeloid for white blood cells, megakaryocytic for platelets). The lymphocytes, which are involved in lymphoproliferative disorders, are usually spared.

Currently, 2 definitive treatments are available for patients with severe AA: immuno-suppressive therapy (IST) that includes the use of anti-thymocyte globulin, cyclosporine, and cyclophosphamide; and allogeneic bone marrow transplantation (ABMT). Allogeneic bone marrow transplantation from human leukocyte antigen (HLA)-matched, related donors is generally accepted as the initial treatment of choice for young patients (less than 20 years old).

For patients older than 40, the generally accepted treatment of choice is IST, which entails the combination of anti-thymocyte globulin and cyclosporin A. A variable proportion of patients (ranging from 20 to 80 %) respond to IST. However, although responses may be frequent, long-term outcome is guarded because some patients may relapse and others may develop a clonal disorder, including myelodysplasia, leukemia, or paroxysmal nocturnal hemoglobinuria

(See Appendix A)

Hematopoietic cell transplantation (HCT) with an HLA-identical sibling currently is the treatment of choice for a child with severe aplastic anemia (SAA) because it offers a cure by restoration of normal hematopoiesis and is associated with low mortality and morbidity.

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 ~~OR any active form of~~ any ~~ONE~~ 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
e. Dental exam and x-rays to identify and treat potential sources of infection from the oral cavity

6. Karnofsky rating 70% or greater and/or Eastern Cooperative Oncology Group (ECOG) performance status less than 2
7. Documentation of member's ability to understand the risks of the procedures.
8. Emotional and psychiatric stability, including a strong family or alternative support network (documented by formal social work evaluation)
9. 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 when the member meets the criteria for **severe aplastic anemia (SAA)** as follows:

- A marrow biopsy showing less than 25 percent of normal cellularity, *or*
- A marrow showing less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present:
    - Absolute reticulocyte count below 40,000/microL (or less than 1%);
    - Absolute neutrophil count (ANC) less than 500/microL; or
    - Untransfused platelet count below 20,000/microL.

Meridian considers allogeneic hematopoietic cell transplantation medically necessary for **Fanconi's Anemia** when the member has:

- Severe aplastic anemia (see criteria above for severe aplastic anemia) *or*
- Myelodysplastic syndrome *or*
- Acute Myelogenous Leukemia

Meridian considers allogeneic hematopoietic cell transplantation medically necessary for **Diamond-Blackfan Anemia** when the member has been:

- Refractory to corticosteroids

Meridian considers allogeneic hematopoietic cell transplantation medically necessary for **Paroxysmal Nocturnal Hemoglobinuria** when the member has:

- Severe aplastic anemia (see criteria above for SAA)
- Ongoing transfusion requirements and
- HLA-matched donor *or*
- Has Myelodysplastic syndrome

Meridian considers allogeneic hematopoietic cell transplantation medically necessary for the treatment of pure red cell aplasia when the member has the following features:

- A marrow biopsy showing cellularity less than 25 % (markedly hypocellular); and
- Absolute reticulocyte count below 40,000/microL (or less than 1 %)

*Criteria for **Autologous** Hematopoietic Cell Transplantation*

Meridian considers autologous hematopoietic cell transplantation **experimental** for the treatment of severe aplastic anemia, pure red cell aplasia, Diamond-Blackfan Anemia, Fanconi's Anemia, and Paroxysmal Nocturnal Hemoglobinuria as its effectiveness has not been recognized and as there is difficulty in obtaining sufficient numbers of normal stem cells.

Repeat Transplant:

A second or repeat allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplant due to persistent, progressive or relapsed disease is considered **investigational** and not medically necessary.

Absolute Contraindications:
Non myeloablative allogeneic Hematopoietic Cell Transplantation (HCT):
Meridian does not cover non myeloablative allogeneic HCT for aplastic anemia as its effectiveness has not been recognized and is considered experimental.

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):

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), 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: ☒
MI:
IL:
OH:

References:

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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:	I.07				

APPENDIX A: "Algorithm treatment of sever aplastic anemia." UpToDate.