POLICY AND PROCEDURE MANUAL

Policy Title: Hematopoietic Cell Transplantation in Beta Thalassemia Major	**Policy Number: F.27**
Primary Department: Medical Management	**NCQA Standard: N/A**
Affiliated Department(s): N/A	**URAC Standard: N/A**
Last Revision Date: 01/31/2019 **Revision Dates: 01/23/2015; 01/08/2016; 02/24/2017; 01/26/2018; 01/31/2019** **Effective Date: 03/27/2015**	**Next Review Date: 03/31/2020** **Review Dates: 03/27/2015; 03/25/2016; 03/31/2017; 03/28/2018; 03/20/2019**
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 ☒	

Policy:
Thalassemia is a congenital hemolytic disease that which consists of a group of disorders with errors in hemoglobin metabolism. It is caused by a partial or complete deficiency of alpha- or beta-globin chain synthesis. Clinical severity ranges from minimal in individuals who are heterozygous carriers of the trait for alpha-thalassemia (i.e., thalassemia minor) to fatal anemia or fatal sequelae of cardiac iron deposits in homozygous beta-thalassemia (i.e., thalassemia major). Conventional treatments for thalassemia include transfusions, splenectomy, and use of medications that increase mobilization and excretion of iron deposits.

Although transfusions and regular iron chelation by means of deferasirox (Exjade) or deferoxamine (Desferal) can extend life expectancy, they are not curative and the disease will be eventually fatal. Allogeneic bone marrow transplant is a curative therapeutic option for patients with thalassemia major. Clinicians are recommended to follow the current practice recommendation of human leucocyte antigen (HLA) typing all individuals with thalassemia, together with their parents and siblings and when an HLA matched donor is available. Outcomes following transplantation from human leukocyte antigen (HLA)-matched donors are influenced by the presence of risk factors such as hepatomegaly, portal fibrosis, and ineffective chelation therapy prior to transplantation. HSCT is highly recommended in people with class 1 and 2 thalassaemia. (Isgro 2010; Lucarelli 2012). See Appendix 1 and 2.

The impact of iron overload is evaluated by the Pesaro risk stratification system which classifies patients with thalassemia who are to undergo allogeneic HSCT into risk groups I through III on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class I having no risk factors, II with 2 risk factors, and III with all 3) .

See Appendix 1 and 2

A human leukocyte antigen (HLA)-identical sibling without thalassemia is the ideal HCT donor. For those who do not have an HLA-matched sibling, a matched unrelated donor (MUD) can often be identified from a donor registry.

Use of alternative donors (those other than a matched sibling or MUD) is considered investigational/experimental by most experts. Some examples of alternate donors considered investigational /experimental include:

- In vitro fertilization with embryo selection to produce an HLA-matched sibling without thalassemia who can donate umbilical cord blood
- Use of a haploidentical-related donor, such as an HLA-mismatched sibling or parent: HSCT should still be considered an experimental approach and should be conducted only in the context of well-designed clinical trials
- Use of unrelated donor umbilical cord blood: UCBT in thalassaemia should only be considered in low risk patients and if the cord blood unit is HLA compatible and contains an appropriate cell number, in the context of well-designed experimental clinical trials.
- Autologous transplant with gene therapy: currently used in clinical trials only

Myeloablative conditioning regimens (without irradiation) should always be used for standard transplantation. Reduced-toxicity regimens are under investigation and may be used in the context of experimental clinical trials.

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 for members with beta-thalassemia*: Member must have a HLA-matched sibling as a donor or HLA-molecularly-matched unrelated donor and all of the following;

- Thalassemia major *and*
- Individuals less than or equal to 30 years of age *and*
- The presence of minimal or no portal fibrous or active hepatitis and
- Member has undergone rigorous medical therapy (transfusion plus high-quality iron chelation therapy)

Absolute Contraindications:
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.

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: ☒

MI:

IL:
OH:

References:

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2. Locatelli F, Rocha V, Reed W, et al. Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease. Blood. 2003; 101(6):2137-2143.
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4. Lucarelli G, Polchi P, Izzi T, et al. Allogeneic marrow transplantation for thalassemia. Exp Hematol 1984; 12:676.
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10. Lucarelli 2012. Lucarelli G, Isgro A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. *Cold Spring Harbor perspectives in medicine* 2012;2. (5):a011825. [PUBMED: 22553502]
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12. Annu Rev Med. 1995;46:319-30. Bone marrow transplantation in thalassemia. Giardini C[1], Galimberti M, Lucarelli G.
13. Nicosia (CY): Thalassaemia International Federation; 2014.n. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 3rd editio Cappellini MD, Cohen A, Porter J, et al., editors
14. Angelucci Emanuele , MD Section Editor:Robert S Negrin, MD Deputy Editor:Jennifer S Tirnauer, MD , Hematopoietic cell transplantation for transfusion-dependent thalassemia, uptodate.com, Literature review current through: Dec 2017
15. Hematopoietic cell transplantation for transfusion-dependent thalassemia. UptoDate.com. Literature review current through: Dec 2018. This topic last updated: Jan 16, 2019.

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

Appendix 1. Lucarelli staging

1.	Absence of hepatomegaly (enlarged liver), regular iron chelation before transplant, absence of fibrosis in pretransplant liver biopsy result
2.	Hepatomegaly, a history of irregular iron chelation before transplant, histological evidence of liver fibrosis, or various combinations of the above
3.	All of the following: large liver, poor compliance with chelation therapy, liver damage
4.	Class 2 or 3, irregular iron chelation, with a range of clinical symptoms and other diagnoses

Appendix 2

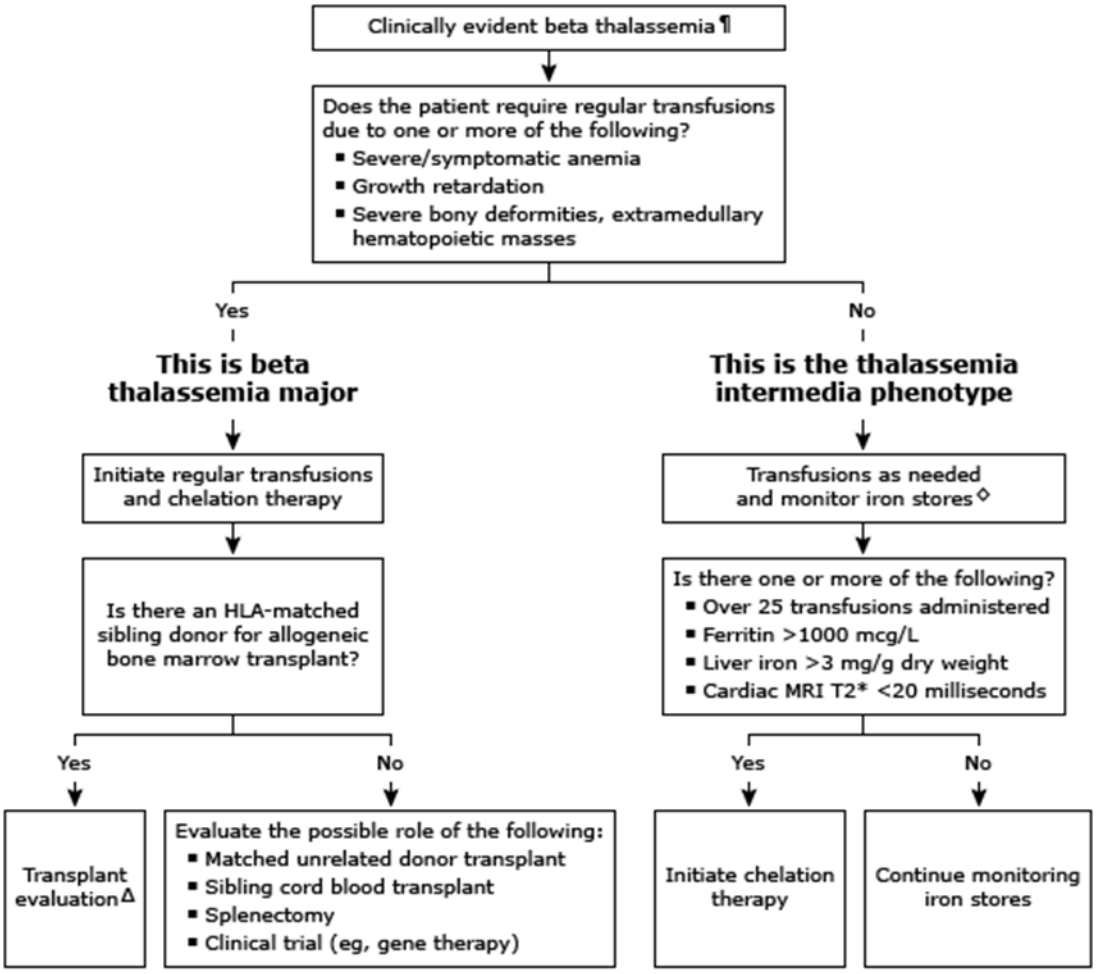
Pessaro Risk Stratification: Predictive variables of outcome after hematopoietic cell transplantation in pediatric patients with thalassemia

Risk factor	Adverse	Favorable
Hepatomegaly (cm from costal arch)	>2 cm	≤2 cm
Liver fibrosis	Presence	Absence
Iron chelation therapy	Irregular	Regular

Risk class

- Class I patients have all three favorable risk factors
- Class II patients have one or two adverse risk factors
- Class III patients have all three adverse risk factors

Algorithm for evaluation of beta thalassemia



Coding Information: The following list of codes is not all inclusive and is to be used as a reference only. The presence of a code in the following table does not imply that the code is covered or non-covered. Final coverage is determined by the State Manual or Benefit Document.

CPT	Description
Collection Codes	
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
Cell Processing Services	
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
Cell infusion codes	
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

ICD-10	Description: [For dates of service on or after 10/01/2015]
D56.0-D56.9	Thalassemia