

# Clinical Policy: Allogenic Hematopoietic Cell Transplants for Sickle Cell Anemia and $\beta$ -Thalassemia

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Coding Implications

Revision Log

## Description

This policy describes the medical necessity requirements for allogenic hematopoietic cell transplants for sickle cell anemia and  $\beta$ -thalassemia. Sickle cell anemia and  $\beta$ -thalassemia are two hemoglobinopathies caused by deleterious genetic alterations in hemoglobin. These monogenic diseases present a range of heterogeneous symptoms that stem from damaged red blood cell function. Despite its limitations, allogenic hematopoietic cell transplants are the only curative therapies possible for these hemoglobinopathies.

## Policy/Criteria

- I. It is the policy of PA Health & Wellness (PHW) that allogenic hematopoietic cell transplants for sickle cell anemia and homozygous  $\beta$ -thalassemia are **medically necessary** when all the following criteria are met:
  - A. *Sickle Cell Anemia*, meets all:
    1. Age  $\leq$  45 years(children and young adults);
    2. HLA-matched, first degree relative donor is available;
    3. History of stroke or is at risk of stroke or end-organ damage, as shown by at least one of the following: prior stroke, recurrent chest syndrome, recurrent vaso-occlusive crises, or red blood cell alloimmunization on chronic transfusion therapy;
  - B. *Homozygous  $\beta$ -Thalassemia*, meets all:
    1. Age  $\leq$  45 years (children and young adults)
    2. HLA-matched donor is available, one of the following:
      - a. Cord blood is the source of stem cells, and the donor is a first-degree relative;
      - b. Bone marrow is the source of stem cells;
      - c. Peripheral blood is the source, and the donor is either unable to, or refuses to donate bone marrow;
    3. Transfusion-dependent due to thalassemia;
    4. A standard, myeloablative conditioning regimen will be used;
    5. Request is made by, or in consultation with, a specialist in treating thalassemia.
- II. It is the policy of PHW that the following are considered **insufficient evidence** regarding the safety and efficacy of the following :
  - A. Autologous hematopoietic cell transplant for sickle cell anemia;
  - B. Autologous hematopoietic cell transplant for  $\beta$ -thalassemia;
  - C. Allogeneic hematopoietic cell transplants for the treatment of sickle cell anemia or homozygous  $\beta$ - Thalassemia for any other indications than those specified above.

## Background

Hemoglobinopathies are a group of over 1,000 hematological disorders that result from deleterious molecular alterations to hemoglobin and are broadly classified into two categories based on the phenotypic characteristics of these variations.<sup>1</sup> The first of these categories

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includes disorders, such as sickle cell anemia, in which there is a structural defect in one of the globin subunits.<sup>1</sup> Thalassemia belongs to the second category of hemoglobinopathies in which there is a quantitative defect in the production of one or more of the globin subunits.<sup>1</sup>

In adults, hemoglobin is a heterotetramer that is comprised of the  $\alpha$ - and  $\beta$ -globin subunits.<sup>2</sup> Each globin subunit forms a stable linkage with heme so that oxygen in the cytosol of an erythrocyte can bind reversibly to heme's iron atoms.<sup>2</sup> The hemoglobin tetramer  $\alpha_2\beta_2$  binds and unloads oxygen in a cooperative manner, which maximizes the transport of oxygen to cells.<sup>2</sup> Additional gas transport functions of hemoglobin include the transport of carbon dioxide and nitric oxide.<sup>3</sup> Each of these physiological aspects of hemoglobin are deleteriously affected in the hemoglobinopathy disorders.

#### *Sickle Cell Anemia and $\beta$ -Thalassemia*

Sickle cell disease results from a synonymous mutation that exchanges glutamic acid with valine at position 6 in the  $\beta$ -globin subunit.<sup>4</sup> Homozygous inheritance of this mutation results in the disease phenotype, whereas heterozygous carriers do not exhibit clinical disease symptoms; heterozygous carriers are also referred to as sickle cell trait.<sup>4</sup> This amino acid substitution causes deoxygenated hemoglobin to rigid polymers in red blood cells, which ultimately forms the classic sickle-shaped morphology.<sup>2</sup> The sickle red blood cells occlude the microvasculature which leads to tissue hypoxia, infarction, and chronic hemolytic anemia.<sup>4</sup> Thus, sickle cell anemia presents a heterogeneous range of clinical manifestations, including pain, strokes, vaso-occlusive episodes, multi-organ injury, reduced quality of life, and shortened lifespan.<sup>2,4</sup>

Autosomal mutations in the gene encoding the  $\beta$ -globin subunit cause  $\beta$ -thalassemia (also known as thalassemia major or Cooley's anemia).<sup>5</sup> These mutations inhibit the synthesis of  $\beta$ -globin in erythropoietic cells.<sup>2,5</sup> The extent of the molecular basis for these mutations is very heterogeneous because over 200 mutations within the  $\beta$ -globin subunit, ranging from synonymous mutations to deletions.<sup>1</sup> Consequently,  $\alpha$ -globin molecules form toxic aggregates which destroy erythroid precursors through a process called ineffective erythropoiesis.<sup>2,5</sup> Also, individuals with  $\beta$ -thalassemia suffer from anemia due to shortened red blood cell survival, hemolysis anemia.<sup>5</sup>

#### *Hematopoietic Cell Transplantation*

Hematopoietic cell transplantation (HCT) is recognized as the only cure for sickle cell disease, and the success rate for specific pediatric groups has been shown to be 85 – 90%.<sup>4</sup> In the United States, it is estimated that the number of children with homozygous sickle cell anemia is 70,000 – 100,000, of which 5,000 – 7,000 could be eligible for transplantation.<sup>6</sup> A survey of the European Blood and Marrow Transplant and CIBMTR data files that ~1,200 patients in total have received HCT for sickle cell disease, and the 3 year survival rate is ~90% regardless of the source of hematopoietic stem cells.<sup>6</sup> Furthermore, Lucarelli *et al.* and Angelucci *et al.* both have documented the literature for recent reports on outcomes of HCT from HLA-matched donors in cases of  $\beta$ -thalassemia.<sup>8,9</sup> Although stem cell sources and the risk categories of the patients vary, overall survival and thalassemia free survival range from approximately 65% - 90 % among the numerous reports.<sup>8,9</sup>

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The establishment of complete donor-derived erythropoiesis can stabilize function in affected organs, such as the central nervous system and lungs.<sup>7</sup> However, HCT related organ toxicities, graft vs host disease, graft rejection, and donor availability are major limitations of this procedure.<sup>7</sup> Infertility and gonadal failure are two specific morbidities with which HCT is associated.<sup>4</sup> Also, use of fully matched sibling donors as potentially eligible donors is one of the limitations for HCT implementation.<sup>4</sup> However, siblings are preferable HCT donors due to the lowered risk of graft vs host disease.<sup>6</sup>

Other differences between the considerations for HCT for  $\beta$ -thalassemia and sickle cell anemia include key issues for risk factors for transplant-related complications, transplant outcome, and conditioning regimen.<sup>9</sup> The major risk factors when considering HCT for  $\beta$ -thalassemia include age and organ dysfunction due to iron overload, whereas the major risk factors for HCT due to sickle cell anemia are age and history of cerebral events.<sup>9</sup> Control of iron overload and related tissue damage is a significant consideration for HCT for  $\beta$ -thalassemia, while obtaining a cure from chronic inflammation and prevention of sickle cell related organ damage must be considered for sickle cell anemia.<sup>9</sup> Lastly,  $\beta$ -thalassemia patients require an ablative conditioning regimen, whereas a reduced intensity regimen seems to induce stable chimerism and full donor erythropoiesis in sickle cell anemia patients.<sup>9</sup>

### Coding Implications

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CPT®* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

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

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ICD-10-CM Code	Description
D56.1	Beta thalassemia
D57.00- D57.819	Sickle-cell disorders

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed	11/17	11/17
Clarified language in II.C. References reviewed and updated.	02/18	05/18
Sickle cell: specified that donor should be a first-degree relative, and that the conditioning regimen should be myeloablative. Beta thalassemia: added that cord blood is allowed if donated by a first-degree relative, added bone marrow as an acceptable source, and peripheral blood as an acceptable source if the donor is unable or unwilling to donate bone marrow; changed requirement for thalassemia specialist to "provider specializing in thalassemia"	02/19	03/19
Removed I.A. 4. Requirement of a standard, myeloablative conditioning regimen. References reviewed and updated. Specialist review.	05/2020	8/7/2020
Revised ICD-10 code range for sickle cell disorders to codes that expand sickle cell categorization. Removed "member" from policy statement in I. and replaced "member" with "member/enrollee" in all other instances. References reviewed and updated. Specialist review.	8/31/2021	
Annual review. References reviewed, updated, and reformatted. Changed "review date" in the header to "date of last revision" and "date" in the revision log header to "revision date." "Experimental/investigational" verbiage replaced in policy statement with, "there is insufficient evidence regarding the safety and efficacy." Reviewed by specialist.	9/21/2022	

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