

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

Reference Number: CP.MP.108

Date of Last Revision: 11/23

[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### Description

This policy describes the medical necessity requirements for allogeneic 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.<sup>1</sup> Despite their limitations, allogeneic hematopoietic cell transplants are the only curative therapies possible for these hemoglobinopathies.

*Note: For criteria related to Zynteglo, please see CP.PHAR.545 Betibeglogene Autotemcel (Zynteglo).*

*Note: For criteria applicable to Medicare plans, please see MC.CP.MP.108 Allogeneic Hematopoietic Cell Transplants for Sickle Cell Anemia and  $\beta$ -Thalassemia.*

### Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that allogeneic 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 acute 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 provider specializing in treating thalassemia.
  - C. Does not have ANY of the following absolute contraindications:
    1. Infections with highly virulent and/or resistant microbes that are poorly controlled pre-transplant;

**CLINICAL POLICY****Hematopoietic Cell Transplants for Sickle Cell Anemia and  $\beta$ -Thalassemia**

2. Inability to adhere to the regimen necessary to preserve the transplant, even with caregiver support;
3. Active substance use or dependence including current tobacco use, vaping, marijuana use (unless prescribed by a licensed practitioner), or IV drug use without convincing evidence of risk reduction behaviors (unless urgent transplant timelines are present, in which case a commitment to reducing behaviors is acceptable). Serial blood and urine testing may be used to verify abstinence from substances that are of concern.

- II.** It is the policy of health plans affiliated with Centene Corporation that there is insufficient evidence regarding the safety and efficacy of the following:
- A. Autologous hematopoietic cell transplant for sickle cell anemia not in the context of gene therapy;
  - B. Autologous hematopoietic cell transplant for  $\beta$ -thalassemia not in the context of gene therapy;
  - 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 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 having 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

## CLINICAL POLICY

### Hematopoietic Cell Transplants for Sickle Cell Anemia and $\beta$ -Thalassemia

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, hemolytic 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 to 90%.<sup>4</sup> In the United States, it is estimated that the number of children with homozygous sickle cell anemia is 70,000 to 100,000, of which 5,000 to 7,000 could be eligible for transplantation.<sup>6</sup> A survey of the European Blood and Marrow Transplant and CIBMTR data files that approximately 1,200 patients in total have received HCT for sickle cell disease, and the three year survival rate is approximately 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>7,8</sup> Although stem cell sources and the risk categories of the patients vary, overall survival and thalassemia-free survival range from approximately 65% to 90 % among the numerous reports.<sup>7,8</sup>

The establishment of complete donor-derived erythropoiesis can stabilize function in affected organs, such as the central nervous system and lungs.<sup>9</sup> However, HCT related organ toxicities, graft vs. host disease, graft rejection, and donor availability are major limitations of this procedure.<sup>9</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>8</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>8</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>8</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>8</sup>

#### **Coding Implications**

This clinical policy references Current Procedural Terminology (CPT<sup>®</sup>). CPT<sup>®</sup> is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. The following codes are for informational purposes only. They are current at time of review of this policy. Inclusion or exclusion of any codes does

**CLINICAL POLICY**

**Hematopoietic Cell Transplants for Sickle Cell Anemia and  $\beta$ -Thalassemia**

not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

| <b>HCPCS</b><br><b>Codes</b> | <b>Description</b>  |
|------------------------------|---|
| 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 posttransplant care in the global definition |

| <b>Reviews, Revisions, and Approvals</b>  | <b>Revision Date</b> | <b>Approval Date</b> |
|---|----------------------|----------------------|
| Policy developed  | 03/16                | 03/16                |
| 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” | 12/18                | 01/19                |
| Removed I.A. 4. Requirement of a standard, myeloablative conditioning regimen. References reviewed and updated. Specialist review.  | 11/19                | 12/19                |
| 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.  | 10/20                |                      |
| References reviewed and updated.  | 11/20                | 11/20                |
| 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.   | 11/21                | 11/21                |
| Annual Review. References reviewed, updated, and reformatted. Reviewed by internal specialist.  | 10/22                | 10/22                |
| Added contraindication criteria I.C.1. through 4. Removed ICD-10 code table from policy.  | 02/23                | 02/23                |
| Annual review. Added note at end of Description regarding criteria related to Zynteglo. Criterion I.C.3. removed related to lack of adequate  | 10/23                | 10/23                |

Hematopoietic Cell Transplants for Sickle Cell Anemia and  $\beta$ -Thalassemia

| Reviews, Revisions, and Approvals   | Revision Date | Approval Date |
|---|---------------|---------------|
| support system. Expanded Criteria II.A. and Criteria II.B. to specify not in the context of gene therapy. Background updated with no impact on criteria. References reviewed and updated. Reviewed by internal and external specialist. |               |               |
| Added note to policy to refer to MC.CP.MP.108 for Medicare criteria. Added “non-Medicare” to health plans in Policy/Criteria I. and II.   | 11/23         |               |

## References

1. Forget BG, Bunn HF. Classification of the disorders of hemoglobin. *Cold Spring Harb Perspect Med*. 2013;3(2):a011684. Published 2013 Feb 1. doi:10.1101/cshperspect.a011684
2. Sankaran VG, Weiss MJ. Anemia: progress in molecular mechanisms and therapies. *Nat Med*. 2015;21(3):221 to 230. doi:10.1038/nm.3814
3. Schechter AN. Hemoglobin research and the origins of molecular medicine. *Blood*. 2008;112(10):3927 to 3938. doi:10.1182/blood-2008-04-078188
4. Kanter J, Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. *Blood Rev*. 2013;27(6):279 to 287. doi:10.1016/j.blre.2013.09.001
5. Ribeil JA, Arlet JB, Dussiot M, Moura IC, Courtois G, Hermine O. Ineffective erythropoiesis in  $\beta$ -thalassemia. *ScientificWorldJournal*. 2013;2013:394295. Published 2013 Mar 28. doi:10.1155/2013/394295
6. Gluckman E. Allogeneic transplantation strategies including haploidentical transplantation in sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2013;2013:370 to 376. doi:10.1182/asheducation-2013.1.370
7. Lucarelli G, Isgrò A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. *Cold Spring Harb Perspect Med*. 2012;2(5):a011825. doi:10.1101/cshperspect.a011825
8. Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. *Haematologica*. 2014;99(5):811 to 820. doi:10.3324/haematol.2013.099747
9. Shenoy S. Hematopoietic stem-cell transplantation for sickle cell disease: current evidence and opinions. *Ther Adv Hematol*. 2013;4(5):335 to 344. doi:10.1177/2040620713483063
10. Khan S, Rodgers GP. Hematopoietic stem cell transplantation in sickle cell disease. UpToDate. [www.uptodate.com](http://www.uptodate.com). Published February 22, 2023. Accessed September 12, 2023.
11. Ozdogu H, Boga C, Yeral M, et al. Allogenic peripheral stem cell transplantation from HLA-matched related donors for adult sickle cell disease: remarkable outcomes from a single-center trial. *Bone Marrow Transplant*. 2018;53(7):880 to 890. doi:10.1038/s41409-018-0111-y
12. Gilman AL, Eckrich MJ, Epstein S, et al. Alternative donor hematopoietic stem cell transplantation for sickle cell disease. *Blood Adv*. 2017;1(16):1215 to 1223. Published 2017 Jun 28. doi:10.1182/bloodadvances.2017005462
13. Allen ES, Srivastava K, Hsieh MM, et al. Immunohaematological complications in patients with sickle cell disease after haemopoietic progenitor cell transplantation: a prospective, single-centre, observational study. *Lancet Haematol*. 2017;4(11):e553 to e561. doi:10.1016/S2352-3026(17)30196-5

**CLINICAL POLICY****Hematopoietic Cell Transplants for Sickle Cell Anemia and  $\beta$ -Thalassemia**

14. Rangarajan HG, Abu-Arja R, Pai V, Guilcher GMT, Soni S. Outcomes of Unrelated Donor Stem Cell Transplantation with Post-Transplant Cyclophosphamide for Graft-versus-Host Disease Prophylaxis in Patients with Severe Sickle Cell Disease. *Biol Blood Marrow Transplant*. 2018;24(2):413 to 417. doi:10.1016/j.bbmt.2017.10.030
15. Benz EJ, Angelucci E. Management of thalassemia. UpToDate. [www.uptodate.com](http://www.uptodate.com). Published May 03, 2023. Accessed September 13, 2023.
16. Angelucci E, Benz EJ. Hematopoietic cell transplantation for transfusion-dependent thalassemia. UpToDate. [www.uptodate.com](http://www.uptodate.com). Published February 27, 2023. Accessed September 13, 2023.
17. Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. *Cochrane Database Syst Rev*. 2020;7(7):CD007001. Published 2020 Jul 3. doi:10.1002/14651858.CD007001.pub5
18. Ghavamzadeh A, Kasaeian A, Rostami T, Kiumarsi A. Comparable Outcomes of Allogeneic Peripheral Blood versus Bone Marrow Hematopoietic Stem Cell Transplantation in Major Thalassemia: A Multivariate Long-Term Cohort Analysis. *Biol Blood Marrow Transplant*. 2019;25(2):307 to 312. doi:10.1016/j.bbmt.2018.09.026

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.



## CLINICAL POLICY

### Hematopoietic Cell Transplants for Sickle Cell Anemia and $\beta$ -Thalassemia

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

**Note: For Medicaid members/enrollees**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare member/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

©2016 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene<sup>®</sup> and Centene Corporation<sup>®</sup> are registered trademarks exclusively owned by Centene Corporation.