

## MEDICAL POLICY – 5.01.42

# Gene Therapies for Thalassemia

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RELATED MEDICAL POLICIES:

None

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## Introduction

Beta ( $\beta$ ) thalassemia is an inherited blood condition where the body makes less hemoglobin. Hemoglobin is a protein in red blood cells. It carries oxygen to all of the body's cells.  $\beta$ -thalassemia can cause tiredness, slow growth rates, abnormal bone changes, weak bones, abnormal growths on the spinal cord, and heart problems. Common treatments for  $\beta$ -thalassemia include blood transfusions, removing extra iron from the body with drugs, and blood stem cell transplants from a donor. Another way to treat  $\beta$ -thalassemia is with gene therapy. Gene therapy uses a person's own blood stem cells to help change the abnormal gene that causes  $\beta$ -thalassemia to get worse. The altered gene is mixed with a drug and put back in the body through a vein (an infusion). The goal of gene therapy for  $\beta$ -thalassemia is for the person's body to make enough hemoglobin so that blood transfusions are no longer needed. This policy describes when gene therapies may be considered medically necessary for people who have  $\beta$ -thalassemia and need regular red blood cell transfusions.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

Drug	Medical Necessity
<p><b>Casgevvy (exagamglogene autotemcel)</b></p>	<p><b>Casgevvy (exagamglogene autotemcel) is considered medically necessary for individuals with transfusion-dependent <math>\beta</math>-thalassemia if they meet criteria 1 through 8:</b></p> <ol style="list-style-type: none"> <li>1. Individual is 12 to 35 years of age</li> <li>2. Documented diagnosis of <math>\beta</math>-thalassemia by globin gene testing.</li> <li>3. Require regular peripheral blood transfusions to maintain target hemoglobin levels.</li> <li>4. Documented history of receiving transfusions of <math>\geq 100</math> ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with <math>\geq 8</math> transfusions per year in the previous 2 years at the time of treatment decision.</li> <li>5. Karnofsky performance status of <math>\geq 80</math> for adults (<math>\geq 16</math> years of age) or a Lansky performance status of <math>\geq 80</math> for adolescents (<math>&lt; 16</math> years of age).</li> <li>6. Negative serologic test for HIV infection (as per U.S. Food and Drug Administration prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for exagamglogene autotemcel manufacturing).</li> <li>7. Individual does not have:             <ol style="list-style-type: none"> <li>a. Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor.</li> <li>b. T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician.</li> <li>c. Advanced liver disease (meets any one of the following):                 <ol style="list-style-type: none"> <li>i. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal.</li> <li>ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal.</li> </ol> </li> </ol> </li> </ol>



Drug	Medical Necessity
	<ul style="list-style-type: none"> <li>iii. Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis.</li> <li>iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis.</li> <li>d. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m<sup>2</sup>.</li> <li>e. History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant.</li> <li>f. Any prior or current malignancy (except for non-melanoma skin cancers)</li> <li>g. Contraindication to the use of plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients.</li> </ul> <p>8. Individual is clinically stable and eligible to undergo a hematopoietic stem cell transplant</p>
<p><b>Zynteglo (betibeglogene autotemcel)</b></p>	<p><b>Zynteglo (betibeglogene autotemcel) is considered medically necessary for individuals with transfusion-dependent β-thalassemia if they meet criteria 1 through 9:</b></p> <ul style="list-style-type: none"> <li>1. Individual is 50 years of age or younger</li> <li>2. Documented diagnosis of β-thalassemia by globin gene testing.</li> <li>3. Require regular peripheral blood transfusions to maintain target hemoglobin levels.</li> <li>4. Documented history of receiving transfusions of ≥100 ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with ≥8 transfusions per year in the previous 2 years at the time of treatment decision.</li> <li>5. Karnofsky performance status of ≥80 for adults (≥16 years of age) or a Lansky performance status of ≥80 for adolescents (&lt;16 years of age).</li> <li>6. Negative serologic test for HIV infection (as per U.S. Food and Drug Administration prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for betibeglogene autotemcel manufacturing).</li> <li>7. Individual does not have:</li> </ul>



Drug	Medical Necessity
	<ul style="list-style-type: none"> <li>a. Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor.</li> <li>b. T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician.</li> <li>c. Advanced liver disease (meets any one of the following): <ul style="list-style-type: none"> <li>i. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal.</li> <li>ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal.</li> <li>iii. Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis.</li> <li>iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis.</li> </ul> </li> <li>d. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m<sup>2</sup>.</li> <li>e. History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant.</li> <li>f. Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder.</li> <li>g. Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome and familial adenomatous polyposis).</li> <li>h. Active, uncontrolled HCV or HBV infection.</li> <li>i. Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients.</li> <li>j. A white blood cell count less than 3 X 10<sup>9</sup>/L, and/or platelet count less than 100 X 10<sup>9</sup>/L not related to hypersplenism.</li> </ul>



Drug	Medical Necessity
	k. An uncorrected bleeding disorder 8. Individuals <5 years of age must weigh a minimum of 6 kg 9. Individual is clinically stable and eligible to undergo a hematopoietic stem cell transplant

Drug	Investigational
<b>Casgevy (exagamglogene autotemcel), Zynteglo (betibeglogene autotemcel)</b>	<b>All other uses of Casgevy (exagamglogene autotemcel) and Zynteglo (betibeglogene autotemcel) for conditions not outlined in this policy are considered investigational.</b>  <b>Repeat treatment of Casgevy (exagamglogene autotemcel) and Zynteglo (betibeglogene autotemcel) is considered investigational.</b>

Length of Approval	
Approval	Criteria
<b>Initial authorization</b>	<b>Casgevy (exagamglogene autotemcel) or Zynteglo (betibeglogene autotemcel) may be approved as a one-time infusion.</b>
<b>Re-authorization criteria</b>	<b>Repeat treatment of Casgevy (exagamglogene autotemcel) or Zynteglo (betibeglogene autotemcel) is considered investigational.</b>

Documentation Requirements
<p><b>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following if applicable:</b></p> <ol style="list-style-type: none"> <li>1. Documented diagnosis of <math>\beta</math>-thalassemia by globin gene testing.</li> <li>2. Require regular peripheral blood transfusions to maintain target hemoglobin levels.</li> <li>3. Documented history of receiving transfusions of <math>\geq 100</math> ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with <math>\geq 8</math> transfusions per year in the previous 2 years at the time of treatment decision.</li> <li>4. Karnofsky performance status of <math>\geq 80</math> for adults (<math>\geq 16</math> years of age) or a Lansky performance status of <math>\geq 80</math> for adolescents (&lt;16 years of age).</li> </ol>



## Documentation Requirements

5. Negative serologic test for HIV infection (as per US FDA prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for manufacturing).
6. Individual does not have:
  - a. Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor.
  - b. T2\*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician.
  - c. Advanced liver disease (meets any one of the following):
    - i. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal.
    - ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal.
    - iii. Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis.
    - iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis.
  - d. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m<sup>2</sup>.
  - e. History of receiving prior gene therapy or allogeneic hematopoietic stem cell transplant.
  - f. Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder.
  - g. Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome and familial adenomatous polyposis).
  - h. Active, uncontrolled HCV or HBV infection.
  - i. Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients.
  - j. A white blood cell count less than 3 X 10<sup>9</sup>/L, and/or platelet count less than 100 X 10<sup>9</sup>/L not related to hypersplenism.
  - k. An uncorrected bleeding disorder
  - l. Any prior or current malignancy
7. Individuals <5 years of age must weight a minimum of 6 kg
8. Individual is clinically stable and eligible to undergo a hematopoietic stem cell transplant

## Coding



Code	Description
<b>HCPCS</b>	
J3590	Unclassified Biologics (use to report Zynteglo and Casgevy)

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

### Recommended Dose

The minimum recommended dose is 5.0 X 10<sup>6</sup> CD34+ cells/kg of body weight.

### Dosing Limits

1 injection per lifetime

### Other Considerations

- Prophylaxis for hepatic veno-occlusive disease is recommended. Prophylaxis for seizures should be considered.
- Monitor platelet counts until platelet engraftment and recovery are achieved. Individuals should be monitored for thrombocytopenia and bleeding.
- Monitor absolute neutrophil counts after betibeglogene autotemcel infusion. If neutrophil engraftment does not occur administer rescue cells.
- Monitor individuals at least annually for hematologic malignancies for at least 15 years after betibeglogene autotemcel infusion.
- Individuals should not take prophylactic anti-retroviral medications or hydroxyurea for at least 1 month prior to mobilization or the expected duration for elimination of the medications, and until all cycles of apheresis are completed as anti-retroviral medications may interfere with manufacturing of the apheresed cells.



- Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. After betibeglogene autotemcel infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider administration of non-myelosuppressive iron chelators. Phlebotomy can be used in lieu of iron chelation, when appropriate.

## Benefit Application

Casgevy (exagamglogene autotemcel) and Zynteglo (betibeglogene autotemcel) are managed through the medical benefit.

## Evidence Review

### Description

$\beta$ -thalassemia is a genetic hemoglobinopathy that results from defects in  $\beta$ -globin synthesis leading to reduced synthesis or absence of  $\beta$ -globin chains causing impaired production of hemoglobin. The clinical presentation is that of anemia which requires transfusion and multiple downstream sequelae from iron overload. It is estimated that at least 1000 people in the United States have transfusion-dependent  $\beta$ -thalassemia. Betibeglogene autotemcel contains autologous CD34+ hematopoietic stem cells in which functional copies of a modified form of the  $\beta$ -globin gene ( $\beta^A\text{-T87Q}$ -globin gene) have been added. Once the hematopoietic stem cells reengineered with  $\beta^A\text{-T87Q}$  are infused, they engraft in the bone marrow and differentiate to produce red blood cells containing  $\beta^A\text{-T87Q}$  gene that will produce HbA<sup>T87Q</sup> protein (functional gene therapy-derived hemoglobin) at levels that may eliminate or significantly reduce the need for transfusions.

### Background

#### $\beta$ -Thalassemia

It is an inherited blood disorder that occurs as a result of a genetic variant in the HBB gene that codes for the production of  $\beta$ -globin chains. As a result, there is reduced synthesis or absence of  $\beta$ -globin chains leading to impaired production of hemoglobin. The clinical presentation is that of anemia which requires iron supplementation and multiple downstream sequelae from the





disease. These sequelae include growth retardation, skeletal changes (particularly in the face and long bones of the legs), osteoporosis, leg ulcers, and development of extramedullary masses. High output heart failure from anemia is also common without treatment. Without transfusion therapy, such individuals die within the first few years of life, primarily from heart failure or infection.<sup>1</sup>

Life expectancy of individuals with transfusion-dependent  $\beta$ -thalassemia is much lower than population norms. From 2011 to 2021 the median age of death for a person in the US with transfusion-dependent  $\beta$ -thalassemia was 37.<sup>2</sup> Additionally, individuals with transfusion-dependent  $\beta$ -thalassemia report decreased quality of life due to the impact on physical and mental health.<sup>3,4</sup>

All humans have 2 copies of the HBB gene and each copy produces the  $\beta$ -globin protein. Different types of  $\beta$ -thalassemia categorized by genotype are summarized in Table 1. When only 1 HBB gene is affected, the phenotype is less severe and individuals are generally asymptomatic due to compensation from the other normal gene. These individuals are called  $\beta$ -thalassemia minor or carrier. However, if both copies of HBB gene are affected there is a quantitative reduction or absence of  $\beta$ -globin protein. Phenotypes that manifest as a reduction in  $\beta$ -globin chains are referred to as " $\beta$ -thalassemia intermedia" and phenotypes that manifest as absence in  $\beta$ -globin chains are called " $\beta$ -thalassemia major".<sup>5</sup>

More recently, individuals have been classified according to their transfusion status (i.e., transfusion-dependent  $\beta$ -thalassemia or non-transfusion-dependent  $\beta$ -thalassemia). For this evidence review, we will focus on transfusion-dependent  $\beta$ -thalassemia individuals which generally includes " $\beta$ -thalassemia major" but occasionally may include individuals with " $\beta$ -thalassemia intermedia". Clinical studies reviewed define "transfusion dependence" as history of at least 100 mL/kg/year of peripheral red blood cells or  $\geq 8$  transfusions of peripheral red blood cells per year for the prior 2 years. "Transfusion independence" was defined as a weighted average hemoglobin (Hb) of at least 9 g/dL without any transfusions for a continuous period of at least 12 months at any time during the study after infusion of betibeglogene autotemcel.

**Table 1. Different Types of  $\beta$ -Thalassemia<sup>5,6,7</sup>**

Type	Genotype	Description
$\beta$ -thalassemia major (generally transfusion dependent)	$\beta^0/\beta^0$ or $\beta^0/\beta^+$	<ul style="list-style-type: none"> <li>• Presents within the first 2 years of life with severe microcytic anemia (typical hemoglobin 3 to 4 g/dL), mild jaundice, and hepatosplenomegaly</li> </ul>



Type	Genotype	Description
		<ul style="list-style-type: none"> <li>Requires regular red blood cell transfusions and other medical treatments</li> </ul>
Thalassemia intermedia	$\beta^+/\beta^+$	<ul style="list-style-type: none"> <li>Presents at a later age with similar, but milder, clinical signs and symptoms of thalassemia</li> <li>Moderately severe anemia; some may need regular blood transfusion</li> </ul>
Thalassemia minor	$\beta/\beta^0$ or $\beta/\beta^+$	<ul style="list-style-type: none"> <li>Also called “<math>\beta</math>-thalassemia carrier” or “<math>\beta</math>-thalassemia trait”</li> <li>Usually clinically asymptomatic but may have a mild anemia</li> <li>Generally do not require any treatment</li> </ul>

$\beta^0$  refers to no beta globin production;  $\beta^+$  refers to decreased beta globin production.

**Epidemiology**

$\beta$ -thalassemia is one of the most common monogenic disorders, but its incidence varies geographically. Higher incidence and prevalence have been reported among individuals from Mediterranean, Africa, the Middle East, and Southeast Asia. While its occurrence is rare in United States, the pattern shows an increasing trend with migration and is expected to increase in the future. According to Bluebird Bio, approximately 1500 people in the United States currently live with transfusion-dependent  $\beta$ -thalassemia.<sup>8</sup>

**Diagnosis**

The diagnostic pathway for symptomatic thalassemia syndromes (thalassemia major and thalassemia intermedia) in a neonate, infant, or child begins with either recognition of symptoms (anemia, evidence of hemolysis and extramedullary hematopoiesis such as jaundice, skeletal abnormalities, and/or splenomegaly) or may be suspected based on a known family history. Initial laboratory testing includes a complete blood count, review of the blood smear, and iron studies. DNA-based genotyping of globin gene can be done relatively inexpensively, is required for precise diagnosis, and is especially important in carrier detection, prenatal testing, and genetic counseling.<sup>5</sup>



## Treatment

The current standard of care for transfusion-dependent  $\beta$ -thalassemia includes blood transfusion, iron chelation therapies, and allogeneic hematopoietic stem cell transplant.

As per the 2014 Thalassemia International Federation guidelines, transfusion is indicated when hemoglobin levels are less than 7 g/dL on 2 different occasions more than 2 weeks apart, or when hemoglobin levels are greater than 7 g/dL but there are co-occurring complications such as facial changes, poor growth, fractures, or clinically significant extramedullary hematopoiesis. The goal of treatment is to maintain a hemoglobin level of 9 to 10.5 g/dL, which has been shown to promote normal growth, suppress bone marrow activity, and minimize iron accumulation.<sup>9,10</sup> Transfusions are typically required every 2 to 5 weeks to reach this goal but can vary for individuals such as those with heart failure who may require higher target hemoglobin levels.<sup>11</sup> Risks of repeated blood transfusions include transfusion reactions, allergic reactions, hemolytic anemia, transfusion-related acute lung injury, and transfusion-related graft versus host disease and alloimmunization.<sup>12</sup> In the event of alloimmunization, it becomes difficult to find a matched blood and also increases the likelihood of delayed transfusion reactions. However, the main complication from frequent blood transfusions is iron overload.

Iron overload as a result of frequent transfusion results in iron accumulation in the heart, liver, and pituitary gland and can lead to heart failure, cirrhosis, hepatocellular carcinoma, hypothyroidism, hypoparathyroidism, hypogonadism, diabetes, and growth failure.<sup>13</sup> Primary treatment for iron overload is chelation therapy (desferrioxamine, deferasirox, deferiprone) and is typically initiated after 10 to 20 transfusions or when the serum ferritin level rises above 1000 mcg/L.<sup>14</sup> Chelation therapy is associated with side effects such as hearing problems, bone growth retardation and local reactions, gastrointestinal symptoms, arthralgia, and neutropenia. Another limitation of chelation therapy is lack of adherence when infused therapies are used as compared to higher adherence for individuals taking oral therapy.<sup>15</sup>

Hematopoietic stem cell transplant is the only curative treatment with cure rates ranging from 80% to 90% in children who receive human leukocyte antigen-identical sibling transplant.<sup>16</sup> Cure rates in adults are lower with a reported range of 65% to 70%.<sup>17</sup> While the cure rates are high, the main limiting factor for hematopoietic stem cell transplant is lack of a compatible donor. Fewer than 25% of individuals have compatible related or unrelated donors, and transplants with mismatched donors or unrelated umbilical cord blood have a lower success rate.<sup>18</sup> Complications from hematopoietic stem cell transplant include mucositis, infection, graft failure, and graft versus host disease. If available, hematopoietic stem cell transplant should be offered to individuals early in the disease course, prior to the onset of iron overload.<sup>14</sup>



There are no randomized trials comparing hematopoietic stem cell transplant with medical therapy for transfusion-dependent thalassemia.<sup>19</sup> Only a 2017 retrospective case-control study has been published, showing no statistically different overall survival with transplantation versus conventional medical therapy (e.g., transfusions and iron chelation).<sup>17</sup> The Center for International Blood and Marrow Transplant Research reported the results of a retrospective cohort of 1110 individuals with  $\beta$ -thalassemia who received a hematopoietic stem cell transplant between 2000 and 2016. The median age at transplantation was 6 years (range: 1 to 25 years), 61% received transplants with grafts from HLA-matched related donors, 7% from HLA-mismatched related donors, 23% from HLA-matched unrelated donors, and 9% from HLA-mismatched unrelated donors. The results are summarized in [Table 2](#).

**Table 2. Outcomes of Retrospective Cohort of Individuals Who Received Hematopoietic Stem Cell Transplant for  $\beta$ -Thalassemia**

Outcome	Matched Sibling	Matched Unrelated	Mismatched Relative	Mismatched Unrelated
5-year survival	89% (n=677)	87% (n=252)	73% (n=78)	83% (n=103)
Graft failure	8.6% (n=677)	5.2% (n=252)	21.8% (n=78)	10.7% (n=103)
Grade 2-4 acute GVHD	11.9% (n=674)	21.5% (n=251)	35.1% (n=77)	19.8% (n=101)
Chronic GVHD	8.3% (n=627)	8.4% (n=249)	20% (n=70)	23.8% (n=101)

<sup>a</sup>Matched relative representative of matched sibling in this study.

GVHD: graft-versus-host disease

## Zynteglo (betibeglogene autotemcel)

For individuals with transfusion-dependent  $\beta$ -thalassemia who receive betibeglogene autotemcel, the evidence includes 2 single-arm studies: HGB-207 (Northstar-2) and HGB-212 (Northstar-3). The Northstar-2 trial enrolled non-  $\beta^0\beta^0$  genotype (less severe phenotype) while Northstar-3 trial enrolled  $\beta$ -thalassemia individuals with either a  $\beta^0$  or  $\beta^+$  IVS1 110 (G>A) variant (severe phenotype) at both alleles of the HBB gene. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related morbidity and treatment-related mortality. The 2 open-label, phase III, single-arm studies included a total of 41 individuals who received a single intravenous infusion of betibeglogene autotemcel. Of the 41 participants, 36 participants in whom transfusion independence was evaluable were included in



the efficacy analysis. Transfusion independence was achieved in 89% (95% CI, 74% to 97%) of study participants. Limitations include a small sample size and limited duration of follow-up. There is uncertainty regarding the durability of effect over a longer time period. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect. The small sample size creates uncertainty around the estimates of some of the individual-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and, as such, may not be observed in small trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about the degree of risk with betibeglogene autotemcel infusion in real-world practice. Insertional oncogenesis has been identified as a potential risk with transgene integration. There has been no evidence of insertional oncogenesis and no malignancies in the trials of betibeglogene autotemcel. However, cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in gene therapy trials that use a lentiviral vector to treat other conditions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Ongoing and Unpublished Clinical Trials

Ongoing trials that might influence this review are listed in [Table 3](#).

**Table 3. Summary of Ongoing and Unpublished Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
<a href="#">NCT02633943</a> <sup>a</sup>	Long-term Follow-up of Subjects With Transfusion-Dependent $\beta$ -Thalassemia Treated With Ex Vivo Gene Therapy	66	November 2035

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National



Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

## **Institute for Clinical and Economic Review**

The Institute for Clinical and Economic Review published a final report on comparative effectiveness and value of betibeglogene autotemcel for beta thalassemia on July 19, 2022.<sup>24</sup> The Report concluded that betibeglogene autotemcel to be incremental or better with moderate certainty of a small or substantial net health benefit (“B+”) versus standard of care.

## **Cooley's Anemia Foundation**

The Children’s Hospital & Research Center Oakland published the standards of care guidelines for thalassemia in 2012.<sup>25</sup> These guidelines have not been updated since they were published.

## **Medicare National Coverage**

There is no national coverage determination.

## **Regulatory Status**

On August 17, 2022, Zynteglo (betibeglogene autotemcel) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult and pediatric individuals with  $\beta$ -thalassemia who require regular red blood cell transfusions.

## **2023 Updates**

Reviewed prescribing information of Zynteglo. Updated Zynteglo criteria to require that the individual does not have an uncorrected bleeding disorder, any prior or current malignancy, or history of advanced liver disease. Also, individuals must be 50 years of age or younger and <5 years must weigh a minimum of 6 kg. Lastly, the individual must be clinically stable and eligible to undergo a hematopoietic stem cell transplant.



## 2024 Updates

Reviewed prescribing information of Zynteglo. Added coverage criteria for Casgevy (exagamglogene autotemcel).

### References

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## History

Date	Comments
12/01/22	New policy, approved November 8, 2022. Policy created with literature review through August 17, 2022. The use of betibeglogene autotemcel is considered medically necessary for individuals with transfusion dependent beta thalassemia when certain conditions are met. Added HCPC code J3590 to report Zynteglo.
08/01/23	Annual Review, approved July 10, 2023. No changes to the policy statements.
12/01/23	Interim Review, approved November 14, 2023, effective for dates of service on or after March 7, 2024, following 90-day provider notification. Updated Zynteglo criteria to require that the individual does not have an uncorrected bleeding disorder or history of advanced liver disease. Also, individuals must be 50 years of age or younger and <5 years must weigh a minimum of 6 kg. Lastly, the individual must be clinically stable and eligible to undergo a hematopoietic stem cell transplant.





Date	Comments
06/01/24	Annual Review, approved May 14, 2024. Added coverage criteria for Casgevy (exagamglogene autotemcel).

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.



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**Language Assistance**

- ATENCIÓN:** si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 844-722-4661 (TTY: 711).
- 注意:** 如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 844-722-4661 (TTY: 711)。
- CHÚ Ý:** Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 844-722-4661 (TTY: 711).
- 주의:** 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 844-722-4661 (TTY: 711) 번으로 전화해 주십시오.
- ВНИМАНИЕ:** Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 844-722-4661 (телетайп: 711).
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- УВАГА!** Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 844-722-4661 (телетайп: 711).
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- 注意事項:** 日本語を話される場合、無料の言語支援をご利用いただけます。844-722-4661 (TTY:711) まで、お電話にてご連絡ください。
- ማስታወሻ:** የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በገጻ ሊያግዝዎት ተዘጋጅተዋል። ወደ ሚከተለው ቁጥር ይደውሉ 844-722-4661 (መስማት ለተሳናቸው: 711)።
- XIYYEEFFANNA:** Afaan dubbattu Oroomiffa, tajaajjila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 844-722-4661 (TTY: 711).
- ملحوظة:** إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 844-722-4661 (رقم هاتف الصم والبكم: 711).
- ਧਿਆਨ ਦਿਓ:** ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 844-722-4661 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।
- ACHTUNG:** Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 844-722-4661 (TTY: 711).
- ໂປດຊາບ:** ຖ້າວ່າ ທ່ານວົາພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ຄ່າສ່ຽງຄ່າ, ຄວນມີພ້ອມໃຫ້ທ່ານ. ໂທສ 844-722-4661 (TTY: 711).
- ATANSYON:** Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 844-722-4661 (TTY: 711).
- ATTENTION:** Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 844-722-4661 (ATS : 711).
- UWAGA:** Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 844-722-4661 (TTY: 711).
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- ATTENZIONE:** In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 844-722-4661 (TTY: 711).
- توجه:** اگر بہ زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 844-722-4661 (TTY: 711) تماس بگیرید.