# Cigna Medical Coverage Policy

**Subject** **Stem-Cell Transplantation for Primary Immunodeficiency Disorders**

**Effective Date** ..... **7/15/2014**
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## Coverage Policy

**Cigna covers allogeneic hematopoietic stem-cell transplantation (HSCT) as medically necessary for the treatment of primary immunodeficiency disorders.**

## General Background

Primary immunodeficiency disorders, also known as congenital or inherited immunodeficiency disorders, are conditions where there is a failure of the immune system to fight invading microorganisms or tumors. The term primary refers to the genetic basis of the defects, differentiating them from secondary, or acquired, immunodeficiencies caused by malnutrition, infection, chemotherapy, or other external agents (Lindegren, 2004). The disorders vary in the severity and spectrum of symptoms, but without effective and early treatment they can be fatal (Lindegren, 2004).

Primary immunodeficiency disorders are often classified according to the affected components of the immune system or immunologic phenotype (Ballow, 2011; Notarangelo, 2006; Lindegren, 2004). Although over 165 primary immunodeficiency syndromes have been identified, less than 20 disorders account for over 90% of the known cases (Ballow, 2011; Lindegren, 2004). Some of the more commonly occurring disorders include the following:

- **B-cell (antibody) deficiencies**
  - X-linked agammaglobulinemia
  - combined variable immunodeficiency (CVID)
  - hyper-IgM syndrome
  - selective IgA deficiency

- **Combined T-cell and B-cell (antibody) deficiencies**
  - severe combined immunodeficiency (SCID)
  - partial combined immunodeficiency (CID)
  - Wiskott-Aldrich syndrome (WAS)

- **T-Cell deficiencies**
  - DiGeorge syndrome

- **Defective phagocytes**
  - Chediak-Higashi syndrome
  - chronic granulomatous disease
  - leukocyte adhesion defect

- **Complement deficiencies**
  - hereditary angioedema

- **Deficiencies/cause unknown**
  - hyper-IgE syndrome
  - chronic mucocutaneous candidiasis

- **Defects in innate immunity**
  - anhidrotic ectodermal hyperplasia (NEMO deficiency)
  - X-linked IgM syndrome

- **Autoinflammatory disorders**
  - tumor necrosis factor (TNF) receptor periodic fever
  - hyper-IgD syndrome

Treatment varies depending on the specific disorder. Allogeneic hematopoietic stem-cell transplantation (HSCT) is a potentially curative treatment option for primary immunodeficiency disorders.

**Stem-Cell Transplantation**
Stem-cell transplantation refers to transplantation of hematopoietic stem-cells (HSC) into an individual. HSC transplantation (HSCT) can be either autologous (using the individual's own stem cells) or allogeneic (using stem cells from a donor). Although allogeneic HSCT is an accepted therapy for primary immunodeficiency disorders, defects in the affected individual's immune system preclude the use of autologous HSCT for this indication.

**Contraindications to Transplantation**
Many factors affect the outcome of a tissue transplant. The selection process is designed to obtain the best result for each individual. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)
- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

**Literature Review**
Data from randomized controlled trials are lacking; however, there are a number of retrospective, observational, and descriptive studies in the published peer-reviewed scientific literature demonstrating safety and improved survival with the use of allogeneic HSCT for the treatment of primary inherited immunodeficiency disorders. Overall survival (OS) varies from 100%–72% at four-, and five-years, respectively, depending on specific

disorder and donor type (Mitchell, 2013; Slatter, 2012; Dinardo, 2011; Petrovic, 2009; Diaz de Heredia, 2008, Cohen, 2007; Sato, 2007).

**SCID:** Allogeneic HSCT is the treatment of choice for SCID variants, as well as for several other inherited immunodeficiencies (Diaz de Heredia, 2008; National Institutes of Health [NIH], 2008; Velardi, 2007). With a human leukocyte antigen (HLA)-identical sibling, the probability of survival approaches 100%. Less favorable results are reported for patients transplanted from an unrelated volunteer or an HLA–partially matched relative. Several retrospective reviews reflect long-term survival of 88%–92.3% (i.e., up to 11 years) (Dinardo, 2012; Friedrich, 2009; Grunebaum, 2006). Use of reduced-intensity conditioning with a human leukocyte antigen (HLA)-identical donor allogeneic HSCT to improve long-term immune reconstitution is an evolving therapy for this condition (Cancrini, 2010). The Primary Immune Deficiency Treatment Consortium (PIDTC) is conducting prospective and retrospective studies assessing overall survival, lineage-specific engraftment, immunologic recovery, current status, and quality of life. Analysis of the variables that affect these outcomes will include patient genotype and phenotype, donor type, donor source, HLA matching, and conditioning received before HCT (Griffith, 2014). Although data are not robust, allogeneic HSCT is an accepted therapy for the treatment of primary immunodeficiency disorders, including SCID.

**Wiskott-Aldrich Syndrome (WAS):** The rarity of WAS and variety of donor sources used (e.g., matched sibling, matched and mismatched unrelated adult hematopoietic stem-cell transplantation (HSCT), haploidentical related, and matched and mismatched cord blood) necessitate cooperative registry studies to analyze even straightforward outcomes such as survival. Complete donor chimerism cures the life threatening manifestations of WAS, including hemorrhage, infection, autoimmunity and malignancy, and can be achieved using myeloablative doses of chemotherapy (Pai, 2010). Several retrospective reviews and an analysis of registry data reflect long-term event-free (EFS) and overall survival (OS) with allogeneic hematopoietic stem-cell transplantation (HSCT) (Moratto, 2011; Ozsahin, 2008; Munoz, 2007, Kobayashi, 2006). In a retrospective analysis of 194 individuals with WAS who received allogeneic HSCT between 1980 and 2009, Moratto et al. (2011) reported an OS of 84% for the study population. Five-year OS for those who received HSCT since 2000 was 89.1%. Stable full donor chimerism was achieved by 72.3% of individuals who survived for at least one year post transplantation. In a multi-center study of 96 patients undergoing allogeneic HSCT, Ozsahin et al. (2008) reported an overall seven-year event-free survival (EFS) of 75%, with EFS rates of 88% and 71%, respectively, for patients with matched sibling, and unrelated donors. Data suggest an improved EFS and OS with allogeneic HSCT for the treatment of WAS.

**Chediak-Higashi Syndrome:** Eapen et al. (2007) performed a retrospective analysis of 35 patients who underwent an allogeneic HSCT. With a median follow-up of 6.5 years, the five-year probability of OS was 62%. Although data are not robust allogeneic HSCT is considered an accepted treatment for primary immunodeficiency disorders, including Chediak-Higashi syndrome.

**Chronic Granulomatous Disease (CGD):** Currently the only curative therapy for CGD is allogeneic HSCT, although this has been infrequently offered due to the risk of procedure-related morbidity and mortality (Kang, 2011). Gungor et al. (2014) evaluated outcomes of 42 individuals with chronic granulomatous disease receiving reduced intensity allogeneic HSCT in a prospective study. The primary endpoints were overall survival (OS), event-free survival (EFS), probabilities of OS and EFS at two years, incidence of acute and chronic graft-versus-host disease (GVHD), achievement of at least 90% myeloid donor chimerism, and incidence of graft failure after at least six months of follow-up. At median follow-up of 21 months OS was 93% and EFS was 89%. Two-year probabilities of OS and EFS were 96% and 91%, respectively. Graft-failure occurred in 5% of patients. The cumulative incidence of acute GVHD (i.e., grade III–IV) was 4% and of chronic GVHD was 7%. Stable chimerism was documented in 93% of surviving patients. Data suggest that allogeneic HSCT with reduced intensity conditioning is safe and effective for this subset of patients.

Tewari et al. (2012) reported results of a retrospective analysis of 12 children with severe CGD who were treated with myeloablative allogeneic HSCT between 1997 and 2010. All patients were alive and disease-free with median follow-up of 70.5 months (range, 12-167 months) at the time of study publication. Donor chimerism was 92-98%. All school-age children returned back to school fulltime within 18 months after transplantation. According to the authors, myeloablative HSCT resulted in correction of neutrophil dysfunction, durable donor chimerism, excellent survival, good quality of life, and low incidence of graft-vs-host disease regardless of graft source. Soncini et al. (2009) reported the long-term survival outcomes of 20 patients with CGD who underwent allogeneic HSCT between 1998 and 2007. All patients engrafted; 90% were alive with normal neutrophil function

at a median of 61 months. Although data are not robust OS and donor chimerism rates suggest the safety and effectiveness of allogeneic HSCT for the treatment of CGD.

**Leukocyte Adhesion Deficiency:** Qasim et al. (2009) retrospectively analyzed the outcomes of 36 children with leukocyte adhesion deficiency that underwent allogeneic HSCT. At a median follow-up of 62 months, overall survival (OS) was 75%. Although data are not robust allogeneic HSCT is considered an accepted treatment for primary immunodeficiency disorders, including LAK.

**Professional Societies/Organizations**
**National Institute of Child Health and Human Development (NICHD):** The NICHD (2008) notes that for several life-threatening immunodeficiencies, bone marrow transplantation offers the chance of a dramatic, complete, and permanent cure.

**National Marrow Donor Program (NMDP):** The NMDP (1996-2014) notes that allogeneic hematopoietic cell transplantation (HCT) is the only potential cure for the severe forms of several immune deficiency diseases: severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, chronic granulomatous disease, leukocyte adhesion deficiency, DiGeorge syndrome, and Kostmann syndrome.

**Use Outside of the US:** No relevant information.

**Summary**
Primary immunodeficiency disorders are a heterogeneous group of disorders that vary in the severity and spectrum of symptoms, but which are ultimately fatal without early and effective treatment. Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only potentially curative treatment for primary inherited immunodeficiency disorders as noted in the published peer-reviewed scientific literature. Uncontrolled cohort and retrospective studies have demonstrated improved long-term overall- and event-free survival. Although the data are not robust, allogeneic HSCT is considered an acceptable treatment option for selected individuals with primary immunodeficiency disorders.

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## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Covered when medically necessary when used to report allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of primary immunodeficiency disorders:**

| **CPT®* Codes** | **Description** |
|---|---|
| 38205 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic |
| 38207 | Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage |
| 38208 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor |
| 38209 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor |
| 38210 | Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-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 |
| 38230 | Bone marrow harvesting for transplantation, allogeneic |
| 38240 | Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor |
| 38242 | Allogeneic lymphocyte infusions |

| HCPCS Codes | Description |
|---|---|
| S2140 | Cord blood harvesting for transplantation, allogeneic |
| S2142 | Cord blood-derived stem cell transplantation, allogeneic |
| 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 or of pre-and post-transplant care in the global definition |



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