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Clinical Policy Bulletin:
Hematopoietic Cell Transplantation for Primary Immunodeficiency Disorders

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Policy

Aetna considers allogeneic hematopoietic cell transplantation medically necessary for the following primary immunodeficiency disorders (PID):

- Cartilage hair hypoplasia
- CD40 ligand deficiency
- Chediak-Higashi syndrome
- Chronic granulomatous disease
- DiGeorge syndrome
- Griscelli syndrome type 2
- Hemophagocytic lymphohistiocytosis
- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)
- Kostmann syndrome (also known as severe congenital neutropenia, autosomal recessive type 3 (SCN3))
- Leukocyte adhesion deficiency type 1
- MHC class II deficiency
- Severe combined immunodeficiency (SCID)
- Severe congenital neutropenia
- Wiskott-Aldrich syndrome (WAS)
- WAS X-linked thrombocytopenia
- X-linked lymphoproliferative syndrome.

Aetna considers autologous hematopoietic cell transplantation for primary immunodeficiency disorders experimental and investigational because its effectiveness
Background

Primary immunodeficiency disorders (PIDs) constitute a group of highly complex congenital disorders, most of which are characterized by poor prognosis with high mortality and morbidity (Al-Ghonaium, 2008). PIDs are genetically heterogenous, affecting distinct components of the innate and adaptive immune system. More than 120 distinct genes have been identified and the World Health Organization lists more than 150 different forms of primary immunodeficiencies (Geha et al, 2007). The most common forms of PID include ataxia telangiectasia, common variable immunodeficiency (CVID), DiGeorge syndrome, hypogammaglobulinemia, IgG subclass deficiency, severe combined immunodeficiency (SCID), selective IgA deficiency, and X-linked agammaglobulinemia (XLA).

Lindegren et al (2004), in a report of the findings of a November 2001 Centers for Disease Control (CDC) workshop convened to discuss means to improve health outcomes among persons with PID, reported that “approximately 100 separate [primary immunodeficiency (PI)] diseases have been described, but less than 20 probably account for greater than 90% of cases. Although diverse, PIDs share the common feature of susceptibility to infection and result in substantial morbidity and shortened life spans. Most important, prompt diagnosis and treatment can now lead to life-saving treatment and result in marked improvements in the quality and length of life for persons with PIDs.” The prevalence of PIDs increases as researchers discover novel immunodeficiency syndromes and as clinicians increasingly recognize and diagnose nuanced presentations of immunodeficiency (Savides and Shaker, 2010).

The goal of HCT in PID is to restore the number and/or function of lymphocytes or phagocytes through selection of matched, related or unrelated donors, or related haploidentical donors to minimize the risk of graft versus host disease (GVHD) and that prophylactic immunosuppression is performed to minimize risk of GVHD (Garcia et al, 2007). Allogeneic stem cell transplantation involves transplanting stem cells, most often obtained from bone marrow, from a compatible donor whereas autologous stem cell transplantation involves the use of stem cells harvested from the patient. Haploidentical donors share a haplotype; having the same alleles at a set of closely linked genes on one chromosome. Donor T-lymphocyte depletion is also performed in haploidentical and unrelated donors (Garcia et al, 2007). Pretransplantation conditioning regimens, method and use of T-cell depletion, and/or GVHD prophylaxis vary widely among transplantation centers (Griffith et al, 2009).
The National Institute of Child Health and Human Development (NICHD) states that “for several life-threatening immunodeficiencies, bone marrow transplantation (BMT) offers the chance of a dramatic, complete, and permanent cure. Since the first BMT was performed in 1968, nearly 1,000 children with PI, including SCID, WAS, leukocyte adhesion defect, and other disorders, have shown a remarkable recovery. They recover from infections, gain weight, and move on to essentially normal lives.” It has also been noted by NICHD that BMT works especially well for SCID (NICHD, 2012).

The first stem cell transplants for PID were performed in 1968 and Filipovich (2008) reports that “significant progress has been made since that time due to (1) the ability to phenotype and quantitate (CD34+) hematopoietic cells, (2) the advent of high-resolution tissue typing, (3) availability of closely matched unrelated donor bone marrow, peripheral blood, stem cells, and cord blood, and (4) the application of reduced intensity conditioning regimens pre-transplant.”

Antoine et al (2003) reported on PID data collected from 37 European stem-cell transplantation registries in 18 countries, with a total of 1082 transplants studied in 919 patients (566 in 473 SCID patients and 512 in 333 non-SCID patients). Four procedures were excluded owing to insufficient data. For SCID patients, 3-year survival was significantly better following HLA-identical than after mismatched transplantation (77% vs 54%; p = 0.002). Survival in these patients improved over time. In the non-SCID study population, 3-year survival after geotypically and phenotypically human leukocyte antigen (HLA)-matched, HLA-mismatched related, and unrelated donor transplantation was 71%, 42%, and 59%, respectively (p = 0.0006). Acute GVHD predicted poor prognosis regardless of donor origin with the exception of related HLA-identical transplantation in SCID. The authors hypothesized that the improvement in survival over time indicates more effective prevention and treatment of disease-related and procedure-related complications such as infections and GVHD, which can be better prevented in the HLA-non-identical setting through use of improved efficiency in T-cell depletion. The authors concluded that the improvement in survival over time indicates more effective prevention and treatment of disease-related and procedure-related complications such as infection and GVHD.

Land et al (2007) reported that the therapeutic options for DiGeorge syndrome (DGS) with profound T-cell deficiency are very limited. Although not readily available, thymic transplantation has shown promising results. The authors further stated that “HCT has been successful in restoring immune competence in the short term”. Land et al conducted a long-term follow-up of 2 patients with complete DGS who received bone marrow transplants in the neonatal period from HLA-matched siblings, and performed a multicenter survey to document the status of other patients with DGS who have undergone HCT. Among reported patients with DGS receiving HCT, the authors found survival was greater than 75% among reported patients with DGS receiving HCT. Their hematopoietic compartment showed continuous engraftment with mixed chimerism, normal T-cell function, and humoral immunity. Thus, the authors concluded that bone marrow transplant in complete DGS using an HLA-matched sibling donor provides long-lasting immunity and is a suitable and more available alternative to thymic transplantation.

Diaz de Heredia et al (2008) studied fifteen PID children with a median age of 11.6 months (SCID 11, X-linked lymphoproliferative syndrome 2, Omenn's syndrome 1, WAS 1), who received an umbilical cord blood (UCB) transplant where the donor was
unrelated in 14 cases and related in 1 case. All patients engrafted and the authors found that eight patients developed acute GVHD grades II-IV and one chronic GVHD, and that viral and fungal infections were frequent. Four patients died during the follow up period, three from GVHD grade IV complicated by infection and one from progressive interstitial lung disease. All surviving patients presented complete immunologic reconstitution with a five year survival rate of 0.73 +/- 0.12 for the overall study population.

Petrovic et al (2009) retrospectively analyzed the transplantation outcomes of 31 patients with PIDs treated from 1986 - 2009 at All Children's Hospital, University of South Florida. Study subjects ranging in age from 1 month to 19 years with SCID, WAS, X-linked hypogammaglobulinemia, and chronic granulomatous disease were included. In 23 patients, the graft source was bone marrow, 4 patients received umbilical cord blood grafts, and 4 patients received peripheral blood stem cell grafts. The authors concluded that better survival rates were observed in those patients transplanted at a younger age and free of infections, demonstrating that transplantation at an early age before significant infections, autoimmune manifestation and malignant transformation have occurred is beneficial.

Friedrich et al (2009) reported on an analysis of 39 WAS patients treated by HCT with a mean follow-up time of 11 years. Fifteen patients received transplants from HLA-identical unrelated donors, 15 from nonidentical parental donors, and 9 from matched siblings, with an overall survival rate is 90% in patients with matched donors and 50% in patients after nonidentical transplantation. Treatment failures in the latter group were mainly related to graft rejections, GVHD, and infections following repeat transplants. Long-term survivors in both patient groups remain with few exceptions, free of late complications and with stable graft function and complete donor cell chimerism. The authors concluded that early and prompt treatment of each diagnosed WAS patient if an HLA-matched, related, or unrelated donor can be identified is recommended. If this is not the case, HLA-nonidentical donor transplantation represents an alternative to be considered early in patients with severe disease.

Griffith et al (2009) described results of a survey conducted by a collaborative network of North American investigators caring for patients with PID. The network of investigators have formed the Primary Immune Deficiency Treatment Consortium (PIDTC), which is a part of the National Institutes of Health Rare Diseases Clinical Research Network (PIDTC, 2012). The PIDTC, although acknowledging the challenges of determining formal guidelines given the rare nature of PID and its many sub-types, are continuing to work toward the development of a database sufficiently robust that evidence-based guidelines can be provided. The PIDTC recommends early diagnosis and definitive therapy for SCID as essential, including referral to a center with experience in HCT. The forms of non-SCID the PIDTC has determined are correctable by means of HCT are presented in Table 1.

Straathof et al (2009) conducted a Phase I/II study of HCT with antibody-based minimal intensity conditioning. The authors stated that stem-cell transplantation can cure primary immunodeficiencies, but in patients with pre-existing organ toxicity, younger than 1 year, or with DNA or telomere repair disorders, chemotherapy-based conditioning is poorly tolerated. They evaluated a minimal-intensity conditioning regimen in 16 high-risk PID patients. The conditioning treatment consisted of antibodies YTH 24.5 and YTH 54.12 combined with alectuzumab, fludarabine, and low dose cyclophosphamide for immunosuppression. Donors were matched siblings, or matched and mismatched unrelated donors. The investigators found that their conditioning regimen was well
tolerated and reported their rates of clinically significant acute (36%) and chronic (31%) GVHD as acceptable. Only one patient required retransplantation. Thus, the authors concluded that their conditioning regimen may reduce toxicity and late effects and enable HCT in virtually any PID patient with a matched donor.

Gennery et al (2010) evaluated the long-term outcome of patients with SCID and non-SCID PID treated between 1968 and 2005. Patients with SCID who had genoidentical donors (n = 25) had survival rates of 90%. Multivariate analysis showed that transplantation after year 1995, younger age, B (+) phenotype, genoidentical or phenoidentical donors, and absence of respiratory impairment or viral infection before transplantation were associated with better prognosis. Non-SCID PID patients using an unrelated donor (n = 124) were found to have a 3-year survival rate similar to that of a genoidentical donor (n = 73), at 76% for both. Survival was 76% in phenoidentical transplants (n = 23) and 46% (n = 47) in mismatched related donor transplants. The authors concluded that individual disease categories should be analyzed to aid in specifying disease-specific prognosis and optimizing treatment planning.

Morio et al (2011) performed UCB transplantation in 88 PID patients. The forms of PID included SCID (n = 40), WAS (n = 23), chronic granulomatous disease (n = 7), severe congenital neutropenia (n = 5), and other immunodeficiencies (n = 13). Five-year overall survival was 69% (95% confidence interval, 57 - 78%). The cumulative incidence of grade 2 - 4 acute GVHD at day 100 was 28% (95% confidence interval, 19 - 38%). The authors concluded that UCB transplantation should be considered for PID patients without an HLA-matched sibling.

Martin-Nalda et al (2011) conducted a retrospective review of 189 PID patients diagnosed in a pediatric tertiary care hospital over a period of 10 years. In all but 2 SCID patients, stem cell transplantation was performed. There were positive outcomes in all but 8 SCID patients (2 prior and 6 after transplantation), 3 WAS patients, 1 complete DiGeorge patient, 1 chronic granulomatous disease patient, and 1 ataxia-telangiectasia patient, who died during follow-up. The authors concluded that the vast majority of patients in this series presented with typical clinical features, reinforcing that education of primary care providers allowing earlier diagnosis of PID leads to proper treatment and monitoring and results in improved prognosis.

Kohn (2010), in discussing autologous stem cell transplantation for PID as an alternative to allogeneic transplantation, stated that use of genetically corrected autologous stem cells represents an alternative treatment for patients with PID and could avoid the immunological risks of allogeneic HCT and confer similar benefits. However, Kohn reports that despite the initial successes that have been achieved utilizing gene therapy as an alternative to allogeneic HCT, there have been some serious complications and that additional challenges remain to the broad application of gene therapy for PID. Kohn further noted that “each specific disorder requires a dedicated effort to produce the relevant reagents, perform the pre-clinical efficacy and safety studies and develop the clinical trial protocol and reagents. These are relatively expensive activities that take several years to bring to fruition. However, the human as well as medical costs incurred by severe PID makes these efforts worthwhile and of high importance.”

Table 1: Management of Non-SCID PIDs

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indication for HSCT</th>
<th>Chimerism</th>
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http://qawww.aetna.com/cpb/medical/data/800_899/0830_draft.html
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<tr>
<th>Condition</th>
<th>Recommended treatment</th>
<th>Chimerism recommendation</th>
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<tr>
<td>Cartilage hair hypoplasia</td>
<td>Recommended in patients with severe T-cell deficiency, especially if MFD or MUD is available. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate. Importantly, HCT will not improve skeletal abnormalities.</td>
<td>Mixed donor chimerism is not expected to have negative consequences in this disease.</td>
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<tr>
<td>CD40 ligand deficiency</td>
<td>HCT is recommended if matched family donor (MFD) is available. Transplants from other donor sources such as a matched unrelated donor (MUD) or haploidentical donors should be strongly considered in the presence of severe disease complications.</td>
<td>Mixed donor chimerism is likely to be beneficial.</td>
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<tr>
<td>Chediak-Higashi syndrome</td>
<td>HCT is recommended if MFD or MUD is available. Haploidentical transplants might also have a role in the management of this disease when clinically appropriate.</td>
<td>Mixed donor chimerism is likely to be beneficial.</td>
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<tr>
<td>Chronic granulomatous disease</td>
<td>HCT is recommended for gp91phox-deficient patients (X-CGD) if MFD is available. Transplants of X-CGD from MUD or of other genetic variants from MFD or MUD are considered in the presence of severe disease complications or poor compliance to medical management. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.</td>
<td>Mixed donor chimerism is likely to be beneficial.</td>
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<td>Griscelli syndrome type 2</td>
<td>HCT from any available donor source is recommended for all patients who have not experienced severe neurologic involvement. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.</td>
<td>Mixed chimerism is sufficient to stabilize disease.</td>
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<tr>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>HCT from any available donor source is recommended as soon as the hemophagocytic syndrome is controlled. Neurologic disease is associated with a poor outcome.</td>
<td>Mixed chimerism with ≥ 20% of donor leukocytes is associated with</td>
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<tr>
<td>Condition</td>
<td>Bone Marrow Transplantation (BMT) from MUD or MFD is recommended</td>
<td>Partial donor chimerism can result in sustained remission of the disease.</td>
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<td>Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)</td>
<td>HCT from MFD or MUD is recommended and should preferably be performed early, before onset of diabetes.</td>
<td>Mixed donor chimerism at even relatively low levels is likely beneficial for infection control and can result in lack of significant symptoms.</td>
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<tr>
<td>Leukocyte adhesion deficiency, Type 1</td>
<td>HCT from MFD or MUD is recommended because of long-term disease risks. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.</td>
<td>Long-term mixed chimerism is undesirable because it is associated with autoimmune complications.</td>
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<td>Wiskott-Aldrich syndrome</td>
<td>HCT from MFD or MUD is recommended. The preferred donors are MFD/MUD (70% to 80% survival) versus haploidentical donors (40% survival).</td>
<td>N/A</td>
</tr>
<tr>
<td>WAS-X-linked thrombocytopenia</td>
<td>The decision to perform HCT might be made based on biomarkers (WAS protein expression levels, response to vaccination, and immune laboratory values) or case-specific clinical reasons.</td>
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<td>X-linked lymphoproliferative syndrome</td>
<td>HCT from MFD or MUD is recommended, preferably before development of lymphoma, hemophagocytic syndrome, or other disease complications. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.</td>
<td>Mixed donor chimerism is likely to be beneficial and is not expected to have negative consequences in this disease.</td>
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<tr>
<td>Severe congenital neutropenia</td>
<td>G-CSF resistance leaves no alternative therapy. MFD or MUD has proven successful in the European experience.</td>
<td>Mixed chimerism might be beneficial.</td>
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<tr>
<td>MHC class II deficiency</td>
<td>Early demise without HCT prompts treatment but poor survival (54% with MFD and 32% with haploidentical donors) at 1 year after HCT.</td>
<td>Mixed chimerism is beneficial.</td>
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Hematopoietic Cell Transplantation for Primary Immunodeficiency Disorders


Ganaiem et al (2013) stated that veno-occlusive disease with immunodeficiency (VODI) is an autosomal recessive disorder of CIDs and hepatic injury. Hematopoietic stem cell transplantation (HSCT) -- the only definitive treatment for CID -- appeared to have a high rate of complications in a previous report. In this study, these investigators described a new group of patients with VODI high-lighting further clinical and immunologic aspects of this disease and re-evaluating the effectiveness of HSCT for the treatment of this disorder. They reviewed clinical data, immunologic features, molecular studies, treatment, and final outcome of 8 kindred members with VODI. The patients described had clinical and immunologic findings consistent with VODI. The molecular studies revealed a new mutation in the SP110 gene. Hematopoietic stem cell transplantation was carried out in 5 patients and was successful in 3. The authors concluded that the diagnosis of VODI should be considered in all patients regardless of ethnicity with a SCID-like presentation, especially with a normal mitogen response, or with signs of hepatic injury. They stated that VODI is a primary immune deficiency, which can be successfully corrected by bone marrow transplantation if applied early in the course of disease using appropriate conditioning.

Mitchell et al (2013) performed a retrospective analysis on the outcomes of 135 HSCTs for PIDs in Australian and New Zealand Children's Hematology Oncology Group transplantation centers between 1992 and 2008. The most common indications for HSCT were SCID, Wiskott-Aldrich syndrome, and chronic granulomatous disease. Five-year overall survival (OS) was 72% for the entire cohort. Disease-specific 5-year OS was 70% for SCID, 81% for Wiskott-Aldrich syndrome, and 69% for chronic granulomatous disease. Transplantation-related mortality (TRM) was 10% at day +100. Transplantation-related mortality and OS were equivalent in recipients of related and unrelated donor transplants. Source of stem cells had no impact on TRM or OS with outcomes following unrelated umbilical cord blood similar to unrelated bone marrow. Interstitial pneumonitis, active cytomegalovirus infection, or veno-occlusive disease were all independent variables that significantly decreased OS. The authors concluded that this large series supported the use of HSCT as curative therapy for a range of PIDs, demonstrating excellent survival after both related and unrelated donor transplantation.

Choi and colleagues (2005) stated that severe congenital neutropenia (SCN) is a hematologic condition characterized by arrested maturation of myelopoiesis at the promyelocyte stage of development. With appropriate treatment using recombinant human granulocyte-colony-stimulating factor (r-HuG-CSF), SCN patients are now surviving longer, but are at increased risk of developing myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). Hematopoietic stem cell transplantation is the only curative option for these patients, but transplantation outcomes after malignant transformation are not well established. These researchers reported results for 6 patients with SCN who underwent HSCT for MDS or AML between 1997 and 2001 at 2 transplant centers. Two patients transplanted for MDS survived; both of these patients were transplanted without being given induction chemotherapy. Four patients, who all received induction chemotherapy for AML prior to HSCT, died. Administering induction chemotherapy prior to HSCT resulted in significant morbidity. Rapid transplantation should be the goal for the SCN patient once the diagnosis of MDS/AML is established. The authors concluded that patients with SCN should be monitored carefully for progression to MDS in order to be treated with HSCT as soon as they have progressed and before developing AML.
Moreover, they stated that for SCN patients who progress to AML, HSCT should still be considered, even though the risks appear to be greater.

Ferry et al (2005) studied the outcome of allogeneic HSCT in patients with SCN. Among 101 cases of SCN included in the French Severe Chronic Neutropenia Registry, 9 patients received HSCT between 1993 and 2003, in 7 institutions. The indications were non-response to G-CSF therapy in 4 cases, bone marrow failure in 1 case, and MDS or leukemia in 4 cases. The conditioning regimen consisted of total body irradiation in 2 cases and chemotherapy alone in the other 7 cases. Seven patients received stem cells from unrelated donors and 2 from identical siblings. Engraftment occurred in all but 1 of the patients; 3 patients died. The respective causes of death were GVHD, infection, and EBV post-transplant lympho-proliferative disease. Six patients are alive and in complete remission, with a median follow-up of 3.1 years. The authors concluded that these findings indicated that HSCT is feasible for patients with SCN who do not respond to G-CSF, who have malignant transformation, or who are at a high risk of malignant transformation, even if an HLA-identical sibling donor is not available.

Welte et al (2006) noted that SCN includes a variety of hematologic disorders characterized by severe neutropenia, with absolute neutrophil counts (ANC) below 0.5 x 10^9/L, and associated with severe systemic bacterial infections from early infancy. One subtype of CN, Kostmann syndrome, is an autosomal recessive disorder, characterized histopathologically by early-stage maturation arrest of myeloid differentiation. Severe congenital neutropenia with similar clinical features occurs as an autosomal dominant disorder and many sporadic cases also have been reported. This genetic heterogeneity suggests that several pathophysiological mechanisms may lead to this common clinical phenotype. Recent studies on the genetic bases of SCN have detected inherited or spontaneous point mutations in the neutrophil elastase gene (ELA2) in about 60% to 80% of patients and, less commonly, mutations in other genes. Acquisition of additional genetic defects during the course of the disease, for example, G-CSF receptor gene mutations and cytogenetic aberrations, indicates an underlying genetic instability as a common feature for all congenital neutropenia subtypes. Data on more than 600 patients with SCN collected by the Severe Chronic Neutropenia International Registry (SCNIR) demonstrated that, regardless of the particular SCN subtype, more than 95% of these patients respond to r-HuG-CSF with ANCs that can be maintained above 1.0 x 10^9/L.

Adverse events include mild splenomegaly, osteoporosis, and malignant transformation into MDS/leukemia. If and how G-CSF treatment impacts on these adverse events is not fully understood. In recent analyses the influence of the G-CSF dose required to achieve neutrophil response (ANC greater than 1,000/microL) in the risk of developing AML has been reported. The authors stated that HSCT is still the only treatment available for patients who are refractory to G-CSF treatment.

Elhasid and Rowe (2010) stated that until further progress will occur in the field of gene therapy, the only curative treatment available in SCN, leukocyte adhesion deficiency, and chronic granulomatous disease is allogeneic HSCT.

Carlsson et al (2011) noted that SCN is an immunodeficiency characterized by disturbed myelopoiesis and an ANC less than 0.5 x 10^9/L. Severe congenital neutropenia is also a pre-malignant condition; a significant proportion of patients develop myelodysplastic syndrome or leukemia. Allogeneic HSCT is the only curative treatment for SCN.
Furthermore, an UpToDate review on “Congenital neutropenia” (Coates, 2014) states that “Hematopoietic cell transplantation (HCT) is curative and should be considered for all patients, particularly those with a high requirement for G-CSF”.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

CPT codes covered if selection criteria are met:

38230
38240

CPT codes not covered for indications listed in the CPB:

38232
38241

HCPCS codes covered if selection criteria are met:

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

ICD-9 codes covered if selection criteria are met:

238.79 Other lymphatic and hematopoietic tissues [X-linked lymphoproliferative syndrome]
258.1 Other combinations of endocrine dysfunction [IPEX]
277.6 Other deficiencies of circulating enzymes [leukocyte adhesion deficiency type 1]
279.05 Immunodeficiency with increased IgM [CD40 ligand deficiency]
279.11 DiGeorge’s syndrome
279.12 Wiskott-Aldrich syndrome
279.2 Combined immunity deficiency [SCID]
287.33 Congenital and hereditary thrombocytopenic purpura [WAS-X-linked thrombocytopenia]
288.01 Congenital neutropenia
288.1 Functional disorders of polymorphonuclear neutrophils [chronic granulomatous disease]
288.2 Genetic anomalies of leukocytes [Chediak-Higashi syndrome]

288.4 Hemophagocytic syndromes [lymphohistiocytosis]

The above policy is based on the following references:


27. Coates TD. Congenital neutropenia. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed July 2014.