Immunodeficiency Disorders
The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. The most severe defects (collectively known as severe combined immunodeficiency or SCID) represents a group of rare, sometimes fatal, congenital disorders characterized by little or no immune response. The defining feature of SCID, commonly known as "bubble boy" disease, is a defect in the specialized white blood cells (B- and T-lymphocytes) that defend us from infection by viruses, bacteria and fungi. Without a functional immune system, SCID patients are susceptible to recurrent infections such as pneumonia, meningitis and chicken pox, and can die before the first year of life. Though invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients.

Stem Cell Transplantation
Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person’s own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA
gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

**RECOMMENDATION**

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director’s designee can approve the requested transplant.

Members must meet UNOS guidelines for transplantation and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

**Pre-Transplant Evaluation:**

Criteria for transplant evaluation include all of the following:

- History and physical examination
- Psychosocial evaluation and clearance:
  - No behavioral health disorder by history or psychosocial issues:
    - if history of behavioral health disorder, no severe psychosis or personality disorder
    - mood/anxiety disorder must be excluded or treated
    - member has understanding of surgical risk and post procedure compliance and follow-up required
  - Adequate family and social support
- EKG
- Chest x-ray
- Cardiac clearance in the presence of any of the following:
  - chronic smokers
  - > 50 years age
  - those with a clinical or family history of heart disease or diabetes
- Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- Neurological exam and clearance for transplant: [ONE]
  - Normal exam by H&P
  - Abnormal neurological exam with positive findings: [ONE]
    - Lumbar puncture normal cytology
    - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- Performance Status: [ONE]
  - Karnofsky score 70-100%; or
  - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- Lab studies:
Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)

*Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:

- If HIV positive all of the following are met:
  - CD4 count >200 cells/mm-3 for >6 months
  - HIV-1 RNA undetectable
  - On stable anti-retroviral therapy >3 months
  - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm)

- If abnormal serology need physician plan to address and/or treatment as indicated
  - UDS (urine drug screen) if patient is current or gives a history of past drug abuse
  - *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated
  - *GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant
- *Mammogram (if indicated or ≥ age 40) with complete workup and treatment of abnormal results as indicated
- *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

*Participating Centers of Excellence may waive these criteria

Criteria for Hematopoietic Allogeneic Stem Cell transplantation (HSCT) Transplantation: 5-29

1. Hematopoietic Allogeneic stem-cell transplantation (HSCT) ablative or non-myeloablative from a human leukocyte antigen (HLA)-matched donor (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or from cord blood when there are no matched sibling or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) is considered medically necessary and may be authorized for the treatment of immunodeficiency disorders when ANY of the following criteria are met: [ALL]

- All pre-transplant criteria are met; and
- Diagnosis of one of the following immunodeficiency disorders (including but not limited to): [ONE]
  - Absent T-cell function:
    - Hemophagocytic Lymphohistiocytosis (HLH)
    - Severe Combined Immunodeficiency (SCID)
    - Wiskott-Aldrich Syndrome (WAS)
X-linked lymphoproliferative syndrome
- Absent or defective natural killer function
  - Chediak-Higashi syndrome
- Absent or defective neutrophil function:
  - Primary granulocyte dysfunction
  - Chronic granulomatous disease
  - Omenn Syndrome
  - Leukocyte adhesion deficiency
  - DiGeorge Syndrome
  - Kostmann Syndrome

AND

- The requesting transplant recipient should not have any of the following **absolute contraindications**:
  - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  - Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
  - Systemic and/or uncontrolled infection
  - AIDS (CD4 count < 200 cells/mm³)
  - Unwilling or unable to follow post-transplant regimen
    - Documented history of non-compliance
    - Inability to follow through with medication adherence or office follow-up
  - Chronic illness with one year or less life expectancy
  - Limited, irreversible rehabilitation potential
  - Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
  - No adequate social/family support

- The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
  - Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
    - Smoking, documentation supporting free from smoking for 6 months
    - Active peptic ulcer disease
    - Active gastroesophageal reflux disease
    - CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
    - Obesity with body mass index of >30 kg/m² may increase surgical risk
  - Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
  - Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation
Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

2. **Hematopoietic Allogeneic stem cell transplantation (ablative or non-myeloablative)** may be authorized after the first prior stem cell transplantation has occurred only one time for members with immunodeficiency disorders who meet all of the above criteria for transplant and have any of the following:[ONE]

- primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; **OR**
- failure to engraft*;
- a suitable allogeneic donor has been identified if applicable

*Note: Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds $5 \times 10^9/L$ or $> ANC500$ at any time after transplantation.\(^{26}\)

**CONTINUATION OF THERAPY**

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Kidney profile within the last 12 months;
  - Cardiac update if history of cardiac disease within two years ($\geq 50$ years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

- If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
  - Authorization letter/documentation from previous insurer;
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Cardiac update if history of cardiac disease within two years ($\geq 50$ years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

**COVERAGE EXCLUSIONS**

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met
2. A second or repeat allogeneic (ablative or non-myeloablative) transplant due to persistent, progressive or relapsed disease
3. Autologous stem cell transplantation
4. A planned tandem allogeneic hematopoietic stem cell transplantation
5. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant

**SUMMARY OF MEDICAL EVIDENCE**

The published medical evidence and outcomes for hematopoietic stem cell transplantation for immunodeficiency disorders in the United States consists of registry data obtained from transplant centers that perform adult and pediatric transplantation and is available from the United Network for Organ Sharing (UNOS) database. Registry data demonstrates graft survival rates and outcomes for stem cell transplantation based on demographic and clinical information.²

There is a large amount of published literature regarding transplant outcomes in immunodeficiency disorders. Two recent studies that show graft survival rates and outcomes for stem cell transplantation are outlined below:

A retrospective analysis by Rousso et al. was conducted of HSCT in children with PID in a tertiary medical center over the period of 1983 to 2012. Participants included 93 children with PID with a median follow-up of 3.6 years (range, 29 d to 21.2 y) after HSCT. The 2-year survival rates after HSCT for children with severe combined immune deficiency, hemophagocytic lymphohistiocytosis/lymphoproliferative disease, Wiskott-Aldrich syndrome, granulocyte defect, and undefined PID were 65.7%±6.8%, 80%±10.3%, 83.3%±15.2%, 75%±12.5%, and 25%±21.7%, respectively. Survival was associated with year of HSCT and matching. The hazard ratio (HR) (95% CI) for HSCT done in 1983 to 1999 compared with 2000 to 2012 and for matched (related and unrelated) compared with mismatched donor were 2.14 (0.99 to 4.653) and 3.07 (1.46 to 6.4), respectively. Survival was not associated with age, sex of the recipient, underlying PID, conditioning regimen, and presence of acute graft-versus-host disease. After adjustment to the underlying PID, donor and use of fludarabine-based conditioning, the HR (95% CI) for HSCT from the year 2000 was 4.69 (range, 1.4 to 15.45). Advances in HSCT over time have improved the survival of children with PID.²

Gungor et al. performed a prospective study in 16 centers in 10 countries worldwide enrolled patients aged 0 to 40 years with CGD treated with RIC HSCT consisting of high-dose Flu, serotherapy or low-dose alemtuzumab, and low-dose (50% to 72% of myeloablative dose) or targeted busulfan administration. Unmanipulated bone marrow or peripheral blood stem cells from HLA-matched related-donors or HLA-9/10 or HLA-10/10 matched unrelated-donors were infused. The primary end points were OS and EFS, probabilities of OS and EFS at 2 years, incidence of acute and chronic GVHD, achievement of at least 90% myeloid donor chimerism, and incidence of graft failure after at least 6 months of follow-up. A total 56 patients (median age 12.7 years) with chronic granulomatous disease were enrolled; 42 patients (75%) had high-risk features (i.e., intractable infections and autoinflammation), 25 (45%) were adolescents and young adults (age 14-39 years). Median time to engraftment was 19 days for neutrophils and 21 days for platelets. At median follow-up of 21 months, OS was 93% (52/56) and EFS was 89% (50/56). The 2-year probability of OS was 96% (95% confidence interval [CI], 86.46 to 99.09) and of EFS was 91% (79.78 to 96.17). Graft-failure occurred in 5% (3/56) of patients. The cumulative incidence of acute GVHD of grade III to IV was 4%
and of chronic GVHD was 7% (4/56). Stable (>/>=90%) myeloid donor chimerism was documented in 52 (93%) surviving patients. 11

**Professional Society Guidelines:** 2 25-28

*The National Marrow Donor Program*: The NMDP recommends HCT at time of diagnosis for immunodeficiency disorders. 2

---

**Coding Information**: The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
</tbody>
</table>

**Cell Infusion Codes**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; autologous</td>
</tr>
<tr>
<td>38242</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions</td>
</tr>
<tr>
<td>38243</td>
<td>Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost</td>
</tr>
</tbody>
</table>

**HCPCS**

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>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</td>
</tr>
</tbody>
</table>
follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

<table>
<thead>
<tr>
<th>ICD-9</th>
<th>Description: [For dates of service prior to 10/01/2015]</th>
</tr>
</thead>
<tbody>
<tr>
<td>279.12</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>279.2</td>
<td>Combined immunity deficiency (severe combined immunodeficiency)</td>
</tr>
<tr>
<td>288.1</td>
<td>Functional disorders of polymorphonuclear neutrophils (chronic granulomatous disease)</td>
</tr>
<tr>
<td>288.2</td>
<td>Genetic anomalies of leukocytes (Chediak-Higashi)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Description: [For dates of service on or after 10/01/2015]</th>
</tr>
</thead>
<tbody>
<tr>
<td>D71</td>
<td>Functional disorders of polymorphonuclear neutrophils (chronic granulomatous disease)</td>
</tr>
<tr>
<td>D76.1</td>
<td>Hemophagocytic lymphohistiocytosis</td>
</tr>
<tr>
<td>D81.0-D81.9</td>
<td>Severe combined immunodeficiency (SCID)</td>
</tr>
<tr>
<td>D82.0</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>D82.3</td>
<td>Immunodeficiency following hereditary defective response to Epstein-Barr virus (X-linked lymphoproliferative disease)</td>
</tr>
<tr>
<td>E70.330</td>
<td>Chediak-Higashi syndrome</td>
</tr>
<tr>
<td>E71.520-E71.529</td>
<td>X-linked adrenoleukodystrophy</td>
</tr>
</tbody>
</table>

**RESOURCE REFERENCES**

**Government Agency**

**Peer Reviewed Publications**
5. Blue Cross and Blue Shield Association. High-Dose Lymphoablative Therapy (HDLT) with or without Stem-Cell Rescue for Treatment of Severe Autoimmune Diseases. TEC Assessment. 2002; 16(14).


**Professional Society Guidelines**

25. National Marrow Donor Program® (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) referral guidelines: Recommended Timing for Transplant Consultation.


Other Resources


   - Holmberg L, Deeg H, Sandmaier B. Determining eligibility for autologous/allogenic hematopoietic cell transplantation.
   - Bonilla F. Severe combined immunodeficiency (SCID): An overview.
   - Bonilla F. Combined immunodeficiencies.


32. Advanced Medical Review (AMR): Policy reviewed by practicing MD board certified in Oncology, Hematology. 4/17/19.

Revision/Review History:

3/8/18: Policy reviewed, clinical criteria has not changed.

9/18/19: Policy reviewed, clinical criteria has not changed. For clarity in the diagnosis section on page 3 & 4, added definitions for, absent T-cell function, absent or defective natural killer function, and absent or defective neutrophil function. Updated references and guideline sections.