

Subject: Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses Lysosomal Storage Disorders		Original Effective Date: 2/2/16
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.¹

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL ^{23 31}

Mucopolysaccharidoses (MPS)

The mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs), also known as mucopolysaccharides. Fragments of partially degraded GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities. These are rare conditions, with an estimated total incidence of all types of MPS of approximately 1 in 20,000 live births. The mucopolysaccharidoses (MPS) disorders are classified as types I (Hurlers Syndrome with three subtypes), II (Hunter), III (Sanfilippo), IV (Morquio), VI (Maroteaux-Lamy), VII (Sly), and IX (Natowicz syndrome). MPS V (formerly Scheie syndrome) and MPS VIII are no longer recognized. The MPS disorders are differentiated clinically by their clinical features and age of presentation and biochemically by their associated enzyme deficiency. These features may not be apparent at birth but progress as storage of glycosaminoglycans affects bone, skeletal structure, connective tissues, and organs. Neurological complications may include damage to neurons as well as pain and impaired motor function. This results from compression of nerves or nerve roots in the spinal cord or in the peripheral nervous system, the part of the nervous system that connects the brain and spinal cord to sensory organs such as the eyes and to other organs, muscles, and tissues throughout the body. Depending on the mucopolysaccharidoses subtype, affected individuals may have normal intellect or may be profoundly impaired, may experience developmental delay, or may have severe behavioral problems. Many individuals have hearing loss and hydrocephalus is common in some of the mucopolysaccharidoses. The eye's cornea often becomes cloudy and degeneration of the retina and glaucoma also may affect vision. Currently there is no cure for these disorders. Medical care is directed at

treating systemic conditions and improving quality of life. Enzyme replacement therapies are currently in use for MPS I, MPS II, and MPS VI, and are being tested in the other MPS disorders. Enzyme replacement therapy has proven useful in reducing non-neurological symptoms and pain. Changes to the diet will not prevent disease progression, but limiting milk, sugar, and dairy products has helped some individuals experiencing excessive mucus. A mucopolysaccharidoses (MPS) disorder should be suspected in a child with coarse facial features, hepatosplenomegaly, and bone disease, with or without central nervous system (CNS) abnormalities. However, the initial presentation may be subtle and signs may be variable, depending upon the MPS type and severity, resulting in frequent delays in diagnosis. According to the NIH Mucopolysaccharidoses Fact Sheet, “Bone marrow transplantation (BMT) and umbilical cord blood transplantation (UCBT) have had limited success in treating the mucopolysaccharidoses. Abnormal physical characteristics, except for those affecting the skeleton and eyes, may be improved, but neurologic outcomes have varied. BMT and UCBT are high-risk procedures and are usually performed only after family members receive extensive evaluation and counseling.”²³

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 or 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/OPTN policies and guidelines for pretransplantation evaluation and listing criteria and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

Pre-Transplant Evaluation: ^{29 30 34 36}

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: ^{5-9 14 20 30 32 33 34-36}

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 mucopolysaccharidoses lysosomal storage disorders when ANY of the following criteria are met: **[ALL]**

- All pre-transplant criteria are met; and
- Age ≤ 2 years ^{7 32 33}; and
- Neurologically intact or with moderate cognitive impairment: ³²⁻³³
 - Developmental Quotient (DQ) > 70); and
- Failed conventional therapy if applicable ³²⁻³³ (i.e. diet modification and/or enzyme replacement therapy); and
- Diagnosis of one of the following mucopolysaccharidoses lysosomal storage disorders: **[ONE]**
 - Hurler Syndrome (MPS I): ^{5-7 9 32-33}
 - Hunter Syndrome (MPS II) ^{7 8 14 20}
 - Maroteaux-Lamy Syndrome (MPS VI) ^{7 21}
 - SanFilippo's (MPS III) ⁷

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 < 200cells/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 $>30 \text{ kg/m}^2$ 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 mucopolysaccharidoses lysosomal storage 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*;
- AND**
- 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 $> \text{ANC}500$ at any time after transplantation.³¹*

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 (≥ 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 (≥ 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 EVIDENCE⁵⁻²⁷

The published medical evidence and outcomes for hematopoietic stem cell transplantation for mucopolysaccharidoses lysosomal storage 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

Aldenhoven et al. (2015a) identified predictors of the long-term outcome of patients with MPS-IH after successful HCT. Two hundred seventeen patients with MPS-IH successfully engrafted with a median follow-up age of 9.2 years were included in this retrospective analysis. Primary endpoints were neurodevelopmental outcomes and growth. Secondary endpoints included neurologic, orthopedic, cardiac, respiratory, ophthalmologic, audiologic, and endocrinologic outcomes. Considerable residual disease burden was observed in the majority of the transplanted patients with MPS-IH, with high variability between patients. Preservation of cognitive function at HCT and a younger age at transplantation were major predictors for superior cognitive development post-transplant. A normal α -l-iduronidase enzyme level obtained post-HCT was another highly significant predictor for superior long-term outcome in most organ systems. The long-term prognosis of patients with MPS-IH receiving HCT can be improved by reducing the age at HCT through earlier diagnosis, as well as using exclusively non-carrier donors and achieving complete donor chimerism.⁶

Aldenhoven et al. (2015b) evaluated the survival and graft outcomes of MPS patients receiving HCT according to these guidelines in 2 European centers of expertise. Two consecutive conditioning regimens were used, busulfan/cyclophosphamide or fludarabine/busulfan-based, both with exposure-targeted i.v. busulfan. A noncarrier matched sibling donor (MSD), matched unrelated cord blood (UCB), or matched unrelated donor (MUD) were considered to be preferred donors. If not available, a mismatched UCB donor was used. Participants were 62 MPS patients (56 MPS type I-Hurler, 2 MPS type II, 2 MPS type III, and 2 MPS type VI) receiving HCT at median age 13.5 months (range, 3 to 44). Forty-one patients received a UCB donor, 17 MSD, and 4 MUD. High overall survival (95.2%) and event-free survival (90.3%) were achieved with only low toxicity: 13.3% acute graft-versus-host disease (aGVHD) grades II to IV and 14.8% chronic GVHD (1.9% extensive). A mismatched donor predicted for lower event-free survival ($P = .04$). A higher age at HCT was a predictor for both aGVHD ($P = .001$) and chronic GVHD ($P = .01$). The use of a mismatched donor was a predictor for aGVHD ($P = .01$). Higher rates of full-donor chimerism were achieved in successfully transplanted UCB recipients compared with MSD/MUD ($P = .002$). If complying with the international HCT guidelines, HCT in MPS patients results in high safety and efficacy. This allows extension of HCT to more attenuated MPS types. Because a younger age at HCT is associated with reduction of HCT-related toxicity, newborn screening may further increase safety.⁷

Boelens et al. (2013) reported transplantation outcomes of 258 children with Hurler syndrome (HS) after a myeloablative conditioning regimen from 1995 to 2007. Median age at transplant was 16.7 months and median follow-up was 57 months. The cumulative incidence of neutrophil recovery at day 60 was 91%, acute graft-versus-host disease (GVHD) (grade II-IV) at day 100 was 25%, and chronic GVHD and 5 years was 16%. Overall survival and event-free survival (EFS) at 5 years were 74% and 63%, respectively. EFS after HLA-matched sibling donor (MSD) and 6/6 matched unrelated cord blood (CB) donor were similar at 81%, 66% after 10/10 HLA-matched unrelated donor (UD), and 68% after 5/6 matched CB donor. EFS was lower after transplantation in 4/6 matched unrelated CB (UCB) (57%; $P = .031$) and HLA-mismatched UD (41%; $P = .007$). Full-donor chimerism ($P = .039$) and normal enzyme levels ($P = .007$) were higher after CB transplantation (92% and 98%, respectively) compared with the other grafts sources (69% and 59%, respectively). In conclusion, results of allogeneic transplantation for HS are encouraging, with similar EFS rates after MSD, 6/6 matched UCB, 5/6 UCB, and 10/10 matched UD. The use of mismatched UD and 4/6 matched UCB was associated with lower EFS.⁹

Professional Society Guidelines:²⁸⁻³³

The National Marrow Donor Program: The NMDP recommends HCT at time of diagnosis for Hurler Syndrome (MPS I).³⁰

International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I recommends the following:³²

- All patients with mucopolysaccharidosis I should receive a comprehensive baseline evaluation, including neurologic, ophthalmologic, auditory, cardiac, respiratory, gastrointestinal, and musculoskeletal assessments, and should be monitored every 6 to 12 months with individualized specialty assessments, to monitor disease progression and effects of intervention.

- Patients are best treated by a multidisciplinary team.
- Treatments consist of palliative/supportive care, hematopoietic stem cell transplantation, and enzyme replacement therapy.
- The patient's age (>2 years or < or =2 years), predicted phenotype, and developmental quotient help define the risk/benefit profile for hematopoietic stem cell transplantation (higher risk but can preserve central nervous system function) versus enzyme replacement therapy (low risk but cannot cross the blood-brain barrier).

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.

CPT	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor 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
	Cell infusion codes
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

HCPCS	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 of pre-and post-transplant care in the global definition

ICD-10	Description: [For dates of service on or after 10/01/2015]
E76.01-E76.03	Mucopolysaccharidosis, type I (Hurler's syndrome)
E76.1	Mucopolysaccharidosis, type II (Hunter's syndrome)
E76.2-E76.29	Other mucopolysaccharidoses

RESOURCE REFERENCES

Government Agency

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- National Marrow Donor Program. Inherited Metabolic Disorders Transplant Outcomes. Accessed at: <https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Disease-Specific-Indications-and-Outcomes/Inherited-Metabolic-Disorders/>
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Revision/Review History:

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

6/19/19: Policy reviewed, clinical criteria has not changed, updated references and guidelines.