HEMATOPOIETIC STEM CELL TRANSPLANT

Protocol: TRP011
Effective Date: February 1, 2017

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INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

UNIVERSAL CONTRAINDICATIONS

NOTE: The following list contains the standard contraindications for transplants. These contraindications apply to ALL types of transplants unless otherwise noted. There may be additional contraindications that apply to a specific type of transplant. Please refer to the “Contraindications” section in the specific type of transplant for more information.

This information was obtained from multiple sources in the peer reviewed medical literature. Unless otherwise noted, the following information was obtained from literature authored by Kasiske, Kanaan, Martin et al., Orens et al., and Mehra et al.
Infections
- Acquired Immunodeficiency Syndrome (AIDS) or certain serious and life-threatening diseases that occur in HIV-positive people. These diseases are called "AIDS-defining" conditions. When a person gets one of these illnesses, he or she is diagnosed with the advanced stage of HIV infection known as AIDS. See Appendix for a complete list of these conditions.
- Systemic or uncontrolled infection including sepsis

Significant uncorrectable life-limiting medical conditions

Severe end stage organ damage including but not limited to: Severe diabetes mellitus with end organ damage, irreversible severe pulmonary disease, with FEV1 < 1 L or FVC < 50%, irreversible severe hepatic disease, irreversible severe renal disease

Irreversible, severe brain damage

Social and Psychiatric Issues — It is expected that a patient has demonstrated adherence to all treatment plans and scheduled appointments and there is documentation of a support system and/or caregiver available to provide necessary care. A case should be referred for psychosocial evaluation and/or psychiatry consultation for guidance in any of the following circumstances:
- Emotional instability, significant depression or other psychiatric illness that cannot be controlled that would impact ability to comply with a complex evaluation process, surgical procedure and post-transplant plan of care and/or ability to give informed consent (and does not have a representative/guardian/conservator).
- Limited cognitive ability (memory loss, dementia, etc.) that would impact ability to comply with a complex evaluation process, surgical procedure and post-transplant plan of care and/or ability to give informed consent (and does not have a representative/guardian/conservator).
- Lack of psychosocial support as indicated by either no identified caregiver or an uncommitted caregiver. This would include the lack of transportation to and from transplant related appointments, patient and/or caregiver is unable to adhere to the requirements of transplant related treatment plan. A care contract may be needed.
- Lack of sufficient financial means to purchase post-transplant medications
- History of non-adherence that has not been successfully remediated
- Inability to give informed consent. If the patient has an authorized representative/guardian/conservator or parent in the case of a minor, that individual must understand and support the ongoing health care needs of the patient.

Post-transplant lymphoproliferative disease (PTLD) unless no active disease demonstrated by negative positron emission tomography (PET) scan and resolved adenopathy on computed tomography (CT) and/or magnetic resonance imaging (Blaes, 2009; Khedmat, 2009)

Limited irreversible rehabilitative potential (Bunnapradist, 2007)

REFERENCES


**GENERAL INFORMATION**

- “Back-up” autologous harvesting for patients in complete remission (CR) with no evidence of marrow involvement by malignancy is appropriate. For example, bone marrow or peripheral blood progenitor cell harvesting is appropriate for patients with multiple myeloma in CR and who might be transplanted in the future. Consult benefit document.
- Donor lymphocyte infusion (DLI) following allogeneic stem cell transplant is appropriate for incomplete chimerism and disease relapse in the setting of incomplete chimerism. This is not a second stem cell transplant. (Bacigalupo, 2006)
Repeat stem cell transplant is appropriate for primary and secondary failure to engraft and disease relapse.

Primary failure is the failure to reach three consecutive days with a neutrophil count (absolute neutrophil count/ANC) > 500 μl (0.5 X 10^9/liter) after SCT, while secondary failure is associated with a successful SCT graft where neutrophils increase to > 500 μl (0.5 X 10^9/liter) for at least three consecutive days and subsequently decrease to a lower level until additional treatment is given to obtain engraftment. (There can be a loss of an allogeneic graft with normal blood cell counts due to autologous reconstitution. This can be confirmed with chimerism studies).

Stem cell boost is a Hematopoietic Stem Cell Infusion (HSCI) provided to a transplant recipient to assist with hematopoietic recovery or declining donor chimerism. It is not preceded by a preparative regimen and is not considered a new transplant event. Stem cell boost is a non-standardized term and has been used interchangeably with terms such as reinfusion, support and rescue. For the purposes of this guideline, we endorse use of the term “boost” based on the recommendation of the task force set up by the American Society for Blood and Marrow Transplantation in collaboration with National Marrow Donor Program (LeMaistre, 2013) and the existence of a CPT code for the term boost (CPT 38243).

Autologous stem cell transplant with or without a second autologous transplant (tandem transplant) is considered a standard of care for the treatment of multiple myeloma although controversy does exist particularly in the era of newer and more effective chemotherapy agents such as bortezomib, lenalidomide and thalidomide. (Blade, 2010; Harousseau, 2009; Bashey, 2008; Kumar, 2009) As the primary and salvage treatment for multiple myeloma has become increasingly successful in recent years, it is likely that, going forward, multiple factors will need to be considered prior to making decisions regarding the use of transplantation procedures; e.g., risk stratification, age, comorbidities, etc. and that the role of transplantation may decrease for certain subgroups.

During a tandem transplant, a patient receives two sequential courses of high-dose chemotherapy with stem cell transplant. Peripheral blood hematopoietic stem cells (HSCs) are collected either during recovery of a cycle of induction chemotherapy or after filgrastim mobilization. The patient receives a second preparative regimen, along with hematopoietic progenitor cells (HPCs) collected during the initial mobilization. Both transplantations are planned in advance and typically are performed a few weeks to a few months apart. (LeMaistre, 2013)

Tandem stem cell transplants require review by the Medical Director except for the following conditions: multiple myeloma, testicular germ cell tumors or neuroblastoma, pediatric brain tumors, and other conditions as part of an IRB approved clinical trial.

Third stem cell transplants require Medical Director Review.
- If part of a sequence of high-dose chemotherapy followed by rescue stem cell infusion as is the case with some neuroblastoma, medulloblastoma and testicular germ cell tumor protocols, the entire course may be approved initially.
- Stem cell source and preparative regimens are at the discretion of the treating physician.
- Single unit umbilical cord blood stem cell transplants are standard of care for children in many programs. Children > 45 kg who receive a single cord blood unit may experience prolonged time to engraftment and other post-transplant complications; therefore, a calculation of 2.5 X 10^7 nucleated cells per kilogram may improve response. (de Lima, 2006)
- If a matched related donor is not available AND no donors have been identified through the National Marrow Donor Program (NMDP) OR there is urgency to transplant sooner than would be expected to be possible through a conventional search and harvest of an unrelated donor through the NMDP, the use of stem cells derived from umbilical cord blood or haploidentical donors cells can be authorized under certain circumstances.

- The stem cell transplant expert panels have confirmed that the treatment of any pediatric patient under a Children’s Oncology Group (COG) protocol should be considered Standard of Care.

- Patients who have undergone stem cell transplant have altered immune systems post-transplant. In the case of allogeneic stem cell transplant, the immune system may never fully recover. These patients have unique care needs in the post-transplant period and will require lifelong follow-up and management. (Optum Expert Panel, 2015)

- Chimeric Antigen Receptor Therapy and/or the use of T-cells/natural killer cell protocols provide treatment of the underlying disease and are not considered to be a transplant procedure. Patients receive immune-depleting chemotherapy prior to infusion. Requests for this therapy have been received for such diseases as ALL or neuroblastoma. As it is not a transplant, the review of such requests should be completed by whoever authorizes the medical benefits for the patient and to determine if benefits for participation in a clinical trial exist. (Kalos, 2011)

- The definition of multiple myeloma has been updated. (Rajkumar et al.) As such the diagnoses of frank myeloma, smoldering myeloma and MGUS have changed and can affect indications for treatment. (See Appendix.)

- In an effort to improve outcomes of blood and marrow transplantation, the use of maintenance therapy has received significant attention over the past few years. While it is likely that post-transplant treatment will continue to evolve, there have been a number of maintenance regimens that have demonstrated reasonable effectiveness to merit their coverage when the treating team feels it to be indicated. Covered maintenance therapy regimens include:
  - Rituximab maintenance after autologous transplant for relapsed follicular lymphoma showed a benefit in terms of progression free survival (PFS) though no benefit in overall survival (OS). (Pettengell, 2013)
  - Rituximab maintenance following autologous transplant in patients with perviously untreated Mantle cell lymphoma resulted in an improved PFS but not OS. (Dietrich, 2001)
  - Brentuximab vedotin after autologous stem cell transplantation for patients with Hodgkin’s lymphoma at high risk of relapse or progression showed improved PFS in the AETHERA trial. (Moskowitz et al.) It is reasonable to use in patients who fit into the well-defined criteria of high risk outlined in the Moskowitz et al. paper: primary refractory Hodgkin’s lymphoma, initial remission duration of less than 1-year, and presence of extranodal or advanced-stage disease at time of relapse. Two important risk factors before autologous stem cell transplantation are lack of chemosensitivity to pre autologous stem cell transplantation salvage chemotherapy, and residual disease at the time of high-dose therapy, defined by CT or PET.
  - Immunomodulatory drugs such as thalidomide or lenalidomide, unless a contraindication exists, as recommended by the American Society for Blood and Marrow Transplantation for multiple myeloma. (Shah, 2015)

There is insufficient evidence to support other agents used as maintenance therapy in malignancies other than as described above. Requests for coverage for any other maintenance regimens should be referred to a Medical Director.
Traditionally the treatment of veno-occlusive disease (VOD) has been supportive and the outcomes poor. In March 2016, FDA gave approval to the new drug defibrotide for the treatment of active VOD. At the present time there is not an approved indication for its use in a prophylactic manner which is commonly done overseas in Europe.

- Defibrotide is covered for the treatment of adult and pediatric patients with active hepatic VOD with renal or pulmonary dysfunction following hematopoietic stem cell transplant.
- Defibrotide is not covered for the prevention of VOD

### INDICATIONS

If an indication is listed as “Not standard of care”, the requested service may be covered if there is a state mandate, the member has a cancer clinical trial benefit, can be covered under the CRS program, if there is a life threatening illness clause in the benefit plan, etc. and all provisions of the applicable benefit(s) have been met.

CHECK FOR STATE MANDATES AND THE MEMBER’S BENEFIT PLAN TO DETERMINE ELIGIBILITY.

- ☑ = COVERED INDICATION
- N = NOT A COVERED INDICATION
- □ = If nothing is indicated, this generally means that this is not considered an indication for stem cell transplant of the type requested and we do not expect to see requests for authorization for this particular type of stem cell transplant for this indication. Any requests for stem cell transplant for one of these indications will be referred to the Medical Director for review.

<table>
<thead>
<tr>
<th>Disease/Indication</th>
<th>Auto</th>
<th>Allo</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Lymphoblastic Leukemia (ALL)</td>
<td>☑</td>
<td>☑</td>
<td>Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.</td>
</tr>
<tr>
<td>(Hahn et al., 2005, Oliansky et al. 2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Myeloid Leukemia (AML)</td>
<td>☑</td>
<td>☑</td>
<td>Intermediate and high-risk AML including but not limited to:</td>
</tr>
<tr>
<td>(Oliansky et al., 2007 &amp; 2008)</td>
<td></td>
<td></td>
<td>- First complete response (CR1) with poor-risk cytogenetics or molecular markers</td>
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<tr>
<td></td>
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<td></td>
<td>- AML after relapse</td>
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<td></td>
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<td>- CR2 and beyond</td>
</tr>
<tr>
<td></td>
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<td>See Appendix for the definition of risk markers and clinical risk factors.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.</td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
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<tr>
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</tr>
<tr>
<td><strong>Leukemia</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia (CLL)</td>
<td>N</td>
<td>✓</td>
<td>There is a lack of data supporting auto for CLL; however, the availability of new agents such as idelalisib and ibrutinib, which are highly effective against this condition will likely change how stem cell transplantation is used in this disease. A history of prior treatment should be obtained with every transplant request.</td>
</tr>
<tr>
<td>Chronic Myeloid Leukemia (CML)</td>
<td>N</td>
<td>✓</td>
<td>There are minimal to no data supporting auto in CML. Allo being used much less frequently in the era of tyrosine kinase inhibitors and primarily for the relatively rare very young patients and those exhibiting less than optimal responses to targeted therapy.</td>
</tr>
<tr>
<td>Prolymphocytic Leukemia (Krishnan et al., Kalaycio et al.)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Myelodysplastic &amp; Pre-Leukemic Syndromes (Oliansky et al., 2009)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic Syndrome (MDS)</td>
<td>N</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Myelofibrosis and related conditions (e.g. PRV)</td>
<td>N</td>
<td>✓</td>
<td>Allo approved with Intermediate-2 or High Risk score using the Dynamic International Prognostic Scoring System (DIPSS). See Appendix for DIPSS scoring system.</td>
</tr>
<tr>
<td>Juvenile Myelo-Monocytic Leukemia (JMML/JCML)</td>
<td>N</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Brain Tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic Astocytoma</td>
<td>N</td>
<td></td>
<td>Not standard of care</td>
</tr>
<tr>
<td>Brain stem glioma</td>
<td>N</td>
<td></td>
<td>Not standard of care</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>N</td>
<td></td>
<td>Not standard of care</td>
</tr>
<tr>
<td>Germinoma</td>
<td>N</td>
<td></td>
<td>Not standard of care</td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
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<tr>
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</tr>
<tr>
<td><strong>Brain Tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma Multiforme (GBM)</td>
<td>N</td>
<td></td>
<td>May be considered in infants</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primitive Neuroectodermal Tumor (PNET)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Germ Cell Tumors</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Testicular Germ Cell Tumor</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Extragonadal Germ Cell Tumor</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Seminoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Extragonadal Germ Cell Tumor</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Seminoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Embryonal Carcinoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Mixed Germ Cell Tumors</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Teratoma</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Yolk-Sac Tumor (Endodermal Sinus Tumor)</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Germ Cell Tumor of the Ovary</td>
<td>✓</td>
<td></td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
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<tr>
<td>-------------------------------------------</td>
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</tr>
<tr>
<td><strong>Multiple Myeloma/Plasma Cell Disorders</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td></td>
<td>✓</td>
<td>Refer allograft requests to Medical Director</td>
</tr>
<tr>
<td>a). Single auto</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>b). Tandem (auto followed by auto)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>c). Tandem (auto followed by allo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d). Allogeneic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL-Amyloidosis</td>
<td>✓</td>
<td>N</td>
<td>Allogeneic SCT may be appropriate on clinical trial. Refer to Medical Director</td>
</tr>
<tr>
<td>Waldenstrom Macroglobulinemia</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Monoclonal gammopathy of uncertain significance (MGUS)</td>
<td>N</td>
<td>N</td>
<td>No transplant indicated</td>
</tr>
<tr>
<td>POEM(Polyneuropathy Organomegaly Endocrinopathy, Monoclonal Gammopathy Skin defects Syndrome) (D'Souza et al., Ji et al., Li et al.)</td>
<td>N</td>
<td>N</td>
<td>Autologous SCT may be appropriate. Refer to Medical Director.</td>
</tr>
<tr>
<td>Solitary Plasmacytoma</td>
<td>N</td>
<td>N</td>
<td>No transplant indicated</td>
</tr>
<tr>
<td><strong>Hodgkin’s Lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>✓</td>
<td>✓</td>
<td>Tumor must be chemosensitive which is defined as a complete or partial response based on the Cheson criteria. See Appendix for Cheson criteria.</td>
</tr>
<tr>
<td><strong>Non-Hodgkin’s Lymphoma (NHL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small B-cell lymphocytic lymphoma</td>
<td>N</td>
<td>✓</td>
<td>Auto not standard of care. This is treated in the same manner as CLL. Refer to Medical Director.</td>
</tr>
<tr>
<td>Follicle center lymphoma (Oliansky et al., 2010)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
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<tr>
<td>----------------------------------------------------------------------</td>
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<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma (NHL) (cont)</td>
<td></td>
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</tr>
<tr>
<td>Lymphoplasmacytoid lymphoma/immunocytoma</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marginal zone lymphoma (mucosa-associated lymphoid tissue, splenic, nodal)</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse, large cell lymphoma (mediastinal large cell, primary effusion) (Oliansky et al. 2011)</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precursor B-cell leukemia/lymphoma</td>
<td>✔</td>
<td></td>
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</tr>
<tr>
<td>T-cell Lymphoma</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Teratoid Rhabdoid Tumors</td>
<td>✔</td>
<td>N</td>
<td>Tandem auto may be indicated. May be appropriate as part of a clinical trial. (Nikolaides et al.)</td>
</tr>
<tr>
<td>Blastic Plasmacytoid Dendritic Cell Neoplasm</td>
<td>N</td>
<td>✔</td>
<td>Dietrich et al.</td>
</tr>
<tr>
<td>Epithelial Ovarian Cancer</td>
<td>N</td>
<td>N</td>
<td>Not standard of care</td>
</tr>
<tr>
<td>Ewing Tumor (Ewing Sarcoma)</td>
<td>✔</td>
<td>N</td>
<td>Allogeneic not standard of care</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>✔</td>
<td>N</td>
<td>Tandem auto can be approved</td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>N</td>
<td>N</td>
<td>Not standard of care</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td>N</td>
<td>N</td>
<td>Not standard of care</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>✔</td>
<td>N</td>
<td>Allogeneic not standard of care</td>
</tr>
<tr>
<td>Rhabdomyosarcoma/soft tissue sarcoma</td>
<td>N</td>
<td>N</td>
<td>May be appropriate as part of a clinical trial. (Stiff et al.) Refer to Medical Director</td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
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<tr>
<td>------------------------------------</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Other Malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supratentorial ependymoma</td>
<td>✓</td>
<td></td>
<td>Venkatramani et al.</td>
</tr>
<tr>
<td>Wilms Tumor</td>
<td>✓</td>
<td>N</td>
<td>May be appropriate in relapsed disease as part of a clinical trial (Brown et al., Campbell et al.) Refer to Medical Director</td>
</tr>
<tr>
<td><strong>Hematological Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blackfam-Diamond Syndrome</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Granulomatous Disease</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Agranulocytosis (Kostmann Syndrome)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Amegakaryocytic Thrombocytopenia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskeratosis Congenita</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanconi Anemia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal Nocturnal Hemoglobinuria (PNH)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shwachman-Diamond Syndrome</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalassemia Major</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunodeficiency Syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD40 Ligand Deficiency</td>
<td>N</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Chediak-Higashi Syndrome</td>
<td>N</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>------</td>
<td>------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hemophagocytic Lymphohistiocytosis (HLH) (same as Familial Erythrophagocytic</td>
<td></td>
<td>✓</td>
<td>In addition to classical SCID, there are a variety of severe mixed (B- and T-cell) immune deficiency syndromes, with or without defined genetic abnormalities, which can be treated with allogeneic stem cell transplant.</td>
</tr>
<tr>
<td>Lymphohistiocytosis - FEL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte Adhesion Deficiency</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Omenn Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Severe Combined Immunodeficiency Disease (SCID)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Wiskott-Aldrich Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>X-linked Lymphoproliferative Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Gaucher disease type I (Pastores et al., Charrow et al., Peters &amp; Steward, Jmoudiak &amp; Futerman)</td>
<td>✓</td>
<td></td>
<td>Patients with the non-neuropathic type may benefit from a stem cell transplant following failed enzyme replacement therapy or if significant bone pain exists in spite of enzyme replacement therapy.</td>
</tr>
<tr>
<td>Niemann-Pick type B (Schuchman)</td>
<td></td>
<td>✓</td>
<td>In a non-cerebral form, transplantation may effectively diminish the impact of the accumulation of metabolic byproducts in lung and liver. These patients die from lung and liver disease and are candidates for stem cell transplantation.</td>
</tr>
<tr>
<td>Fucosidosis (Miano et al., Vellodi et al.)</td>
<td>✓</td>
<td></td>
<td>There is little experience with transplantation for fucosidosis, a very rare entity among rare entities, but reports indicate that stem cell transplantation performed early effectively ameliorates disease progression.</td>
</tr>
<tr>
<td>Lysosomal storage diseases (Heese)</td>
<td></td>
<td>✓</td>
<td>Not standard of care. Studies are ongoing. May be considered life threatening if significant end-organ involvement, particularly kidneys and lungs. Refer to Medical Director.</td>
</tr>
</tbody>
</table>

Hematopoietic Stem Cell Transplant
<table>
<thead>
<tr>
<th>Disease/Indication</th>
<th>Auto</th>
<th>Allo</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune Diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>N</td>
<td></td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>N</td>
<td></td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>N</td>
<td></td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>N</td>
<td></td>
<td>Not standard of care. Must be performed under a clinical trial and would only be considered for approval if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td>Systemic Sclerosis (Scleroderma)</td>
<td>N</td>
<td>N</td>
<td>Not standard of care. Studies are ongoing. May be considered life threatening if significant end-organ involvement, particularly kidneys and lungs. Refer to Medical Director.</td>
</tr>
<tr>
<td><strong>Inherited Metabolic Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermolysis Bullosa</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globoid Cell Leukodystrophy (Krabbe Disease)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hurler Syndrome (MPS I)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hunter Syndrome (MPS II)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannosidosis</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maroteaux-Lamy Syndrome (MPS VI)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease/Indication</td>
<td>Auto</td>
<td>Allo</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------</td>
<td>------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Autoimmune Diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MNGIE) Mitochondrial Neurogastrointestinal Encephalopathy (Halter et al., Filosto et al.)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Rett Syndrome</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>N</td>
<td>N</td>
<td>Not standard of care. It would only be considered for approval under a clinical trial if the member’s benefit plan supports participation in a clinical trial.</td>
</tr>
<tr>
<td><strong>Additional Condition/Disease Indications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refer to section titled: Hematopoietic Stem Cell Transplant Reference Sheet</td>
<td>N</td>
<td>N</td>
<td>The reference sheet includes a list of rare and unusual conditions where allogeneic transplant may be indicated. If there is a condition found within this reference that is not included above, refer to Medical Director.</td>
</tr>
</tbody>
</table>

**ORGAN-SPECIFIC CONSIDERATIONS**

Please review the universal Contraindications found at the beginning of the Guidelines. These apply to all transplants unless otherwise noted below. Additional contraindications that are specific to a particular type of transplant are noted below. When a Contraindication is present the transplant will not be approved. Refer to the Medical Director.
- None

**SPECIAL CONSIDERATIONS**

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.
- Cord blood transplants in adults
  - When stem cells are not available from a standard donor source, there may be no reasonable alternative to the use of cord blood units in adults. The available literature supports this approach. In this situation umbilical cord blood SCTs may be approved as standard of care. (Brunstein et al.)
- If participation in a clinical trial is requested, all clinical trial authorization rules will apply.
- Haploidentical stem cell transplants are occurring more frequently due to advances in immunosuppression and the ease of acquiring a donor.
**Hematopoietic Stem Cell Transplant**

- Haploidentical SCT can be approved as an acceptable form of treatment at a center that is FACT-accredited for allogeneic stem cell therapy. (Klingebiel, 2010)

**Multiple Myeloma**

Allogeneic stem cell transplant for multiple myeloma is controversial either as a single allogeneic transplant as initial therapy with curative intent or as the second stage of a planned tandem transplant proceeded by an autologous transplant. The following recommendations are consistent with the evolving practice and recognize the expertise of treating physicians within network programs. The recommendations may change as additional experience is gained with the newer disease modifying agents for the treatment of myeloma and as more experience is gained with reduced intensity allogeneic stem cell transplant for this disease.

**Note:** Refer all requests for allogeneic stem cell transplant in multiple myeloma to Medical Director for review.

- Allogeneic stem cell transplant may be appropriate therapy under the following circumstances
  - Initial therapy in newly diagnosed patients with high-risk disease and in otherwise good health
    - High risk myeloma has been defined by the International Myeloma Working Group (IMWG) based on cytogenetics [Presence of at least one of the following: del(17p), t(4;14) or t(14;16) determined by FISH] and the Mayo Clinic classification adds hypoploidy and t(14;20) to the IMWG definition. Regardless of the source of definition, the requestor should present evidence of sufficient factors that cause the case to be considered high risk.
  - Early relapse (less than 24 months) after primary therapy that included an autologous stem cell transplant or with high-risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they respond favorably to salvage therapy. (Giralt, 2015)
  - Reduced intensity matched related donor (MRD) and matched unrelated donor (MUD) allogeneic SCT as the second transplant of a planned tandem transplant. (Bruno, 2009; Rotta, 2009)
    - The role and choice of maintenance therapy after hematopoietic stem cell transplant is in evolution. It appears to have a role in treatment of residual or relapsed disease or as part of a clinical study to prevent relapse. (Shah, 2015) It can be covered in these situations but any request should be referred to the Medical Director for review.
  - HIV infection
    - Patients should have a formal infectious disease consult indicating adequate treatment and proper assessment of risks related to this transplant
  - Persisting CNS involvement by malignancy except for primary CNS tumors such as those referenced under brain tumor indications.
    - Refer to Medical Director
  - Refer to requesting program Patient Selection Criteria for age specific criteria.
    - If outside the program’s patient selection criteria, refer to Medical Director
  - Serum creatinine < 2.5 mg/dl (≤ 1.5 mg/dl in children) or GFR > 50 ml/min.
    - Serum creatinine may be higher in patients with multiple myeloma or other plasma cell dyscrasias. Patients with multiple myeloma with reduced renal function are not prohibited from undergoing autologous BMT when the decreased renal function is related to the multiple myeloma (myeloma kidney). This includes patients on hemodialysis with no other contraindications.
Pediatric patients should have a Lansky score > 50. Adult patients should have a Karnofsky score > 70. If these criteria not met, refer to Medical Director.

Active untreated or untreatable malignancy in patients undergoing stem cell transplantation for non-malignant indications
- Refer to Medical Director

HEMATOPOIEIC STEM CELL TRANSPLANTATION – TIMING for STEM CELL CONSULTATION

RECOMMENDED TIMING FOR STEM CELL TRANSPLANTATION CONSULTATION


These guidelines for transplant consultation were developed jointly, and updated for 2015, by the National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT). They are based on current clinical practice and the medical literature, including comprehensive evidence based reviews. One critical factor in the outcome of hematopoietic cell transplantation is the appropriate planning and timing of the transplant. The intent of these guidelines is to identify patients at risk of disease progression and, therefore, which patients should be evaluated for transplantation.

While transplant may be immediately indicated for some patients with these factors, it may not be for all patients. The consultation helps ensure there are plans in place for the patient to move quickly to transplant, if needed, before disease progresses or complications develop. If allogeneic transplant is a possibility, it helps provide adequate time for an unrelated donor or cord blood search.

ADULT LEUKEMIAS AND MYELODYSPLASIA

Acute Myelogenous Leukemia (AML)
- High resolution HLA typing is recommended at diagnosis for all patients
- Early after initial diagnosis, all AML patients including:
  - CR1—except favorable risk AML (defined as: t (16;16); inv 16; t (8;21); t (15;17); normal cytogenetics with NPM1 or biallelic CEBPA mutation and without FLT3-ITD)
  - Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))
  - Treatment-related leukemia
  - Primary induction failure or relapse
  - Presence of minimal residual disease after initial or subsequent therapy
  - CR2 and beyond, if not previously evaluated

Acute Lymphoblastic Leukemia (ALL)
- High resolution HLA typing is recommended at diagnosis for all patients
- Early after initial diagnosis, all ALL patients including:
  - CR1
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

**Myelodysplastic Syndromes (MDS)**
- Any intermediate or high IPSS score
- Any MDS with poor prognostic features, including:
  - Treatment-related MDS
  - Refractory cytopenias
  - Adverse cytogenetics
  - Transfusion dependence

**Chronic Myelogenous Leukemia (CML)**
- Inadequate hematologic or cytogenetic response to tyrosine kinase inhibitor (TKI) therapies
- Disease progression
- Intolerance to TKI therapies
- Accelerated phase
- Blast crisis (myeloid or lymphoid)

**Chronic Lymphocytic Leukemia (CLL)**
- High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p); ZAP70, CD38 positivity; unmutated Ig VH mutational status)
- Short initial remission
- Poor initial response
- Fludarabine-resistant
- Richter’s transformation

**PEDIATRIC ACUTE LEUKEMIAS**

**Acute Myelogenous Leukemia (AML)**
- High resolution HLA typing is recommended at diagnosis for all patients
- Early after initial diagnosis, all AML patients including:
  - CR1—except favorable risk AML (defined as: t (16;16); inv 16; t (8;21); t (15;17); normal cytogenetics with PM1 or biallelic CEBPA mutation and without FLT3-ITD)
  - Primary induction failure or relapse
  - Monosomy 5 or 7
  - Age <2 years at diagnosis
  - Treatment-related leukemia
  - Presence of minimal residual disease after initial or subsequent therapy
  - CR2 and beyond, if not previously evaluated

**Acute Lymphoblastic Leukemia (ALL)**
- Infant at diagnosis
- High Risk CR1 including:
  - Philadelphia chromosome positive
- WBC >100,000 at diagnosis
- 11q23 rearrangement
- Mature B-cell phenotype (Burkitt’s lymphoma)
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

LYMPHOMAS
Non-Hodgkin Lymphoma
- Follicular
- Poor response to initial treatment
- Initial remission duration <12 months
- First relapse
- Transformation to diffuse large B-cell lymphoma

Diffuse Large B-Cell or High-Grade Lymphoma
- At first or subsequent relapse
- CR1 for patients with high or high-intermediate IPI risk
- No CR with initial treatment
- Second or subsequent remission

Mantle Cell
- After initiation of therapy

Other High Risk Lymphomas
- After initiation of therapy

Hodgkin Lymphoma
- Primary induction failure or relapse
- Second or subsequent remission

Multiple Myeloma
- All patients after initiation of therapy
- At first progression

OTHER MALIGNANT DISEASES
Germ cell tumors
- Short initial remission
- Poor initial response

Myeloproliferative Disorders (including BCR-ABL–negative myeloproliferative neoplasms, myelofibrosis and later stages of polycythemia vera and essential thrombocytosis)
- Intermediate or high-risk disease including:
  - High-risk cytogenetics
  - Poor initial response or at progression
Neuroblastoma
- Short initial remission
- Poor initial response or at progression

NON-MALIGNANT DISORDERS

Immune Deficiency Diseases (including Severe Combined Immunodeficiency syndromes, Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, Kostmann syndrome)
- At diagnosis

Inherited Metabolic Disorders (including Hurler’s syndrome, adrenoleukodystrophy, and others)
- At diagnosis

HEMAGLOBINOPATHIES

Transfusion-Dependent Thalassemias
- At diagnosis

Sickle Cell Disease
- With aggressive course (end-organ complications, frequent pain crises)

Hemophagocytic Lymphohistiocytosis (HLH)
- At diagnosis

Severe Aplastic Anemia and other marrow failure syndromes (including Fanconi anemia, Diamond-Blackfan anemia, and others)
- At diagnosis

MEDICARE COVERAGE RATIONALE

There is a National Coverage Determination for Stem Cell Transplantation (NCD 110.8.1) Accessed December 2016 and it is as follows:

Stem Cell Transplantation (NCD 110.8.1)
A. General

Stem cell transplantation is a process in which stem cells are harvested from either a patient’s (autologous) or donor’s (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplants (AuSCT) must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic stem cell transplants may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can
undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

**Indications and Limitations of Coverage**

1. **Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**
   Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion

   a. Nationally Covered Indications

   The following uses of allogeneic HSCT are covered under Medicare:

   i. Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,

   ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

   iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

   The MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow.

   Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study. In accordance with the Stem Cell Therapeutic and Research Act of 2005 (US Public Law 109-129) a standard dataset is collected for all allogeneic transplant patients in the United States by the Center for International Blood and Marrow Transplant Research. The elements in this dataset, comprised of two mandatory forms plus one additional form, encompass the information we require for a study under CED.
A prospective clinical study seeking Medicare payment for treating a beneficiary with allogeneic HSCT for MDS pursuant to CED must meet one or more aspects of the following questions:

- Prospectively, compared to Medicare beneficiaries with MDS who do not receive HSCT, do Medicare beneficiaries with MDS who receive HSCT have improved outcomes as indicated by:
  - Relapse-free mortality,
  - progression free survival,
  - relapse, and
  - overall survival?

- Prospectively, in Medicare beneficiaries with MDS who receive HSCT, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:
  - Relapse-free mortality,
  - progression free survival,
  - relapse, and
  - overall survival?

- Prospectively, in Medicare beneficiaries with MDS who receive HSCT, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:
  - Relapse-free mortality,
  - progression free survival,
  - relapse, and
  - overall survival?

In addition, the clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants’ health outcomes.

b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.

c. The research study does not unjustifiably duplicate existing studies.

d. The research study design is appropriate to answer the research question being asked in the study.

e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).

h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.

i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the ClinicalTrials.gov Web site by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than 3 years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, the Agency for Health Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The clinical research study should also have the following features

- It should be a prospective, longitudinal study with clinical information from the period before HSCT and short- and long-term follow-up information.

- Outcomes should be measured and compared among pre-specified subgroups within the cohort.
• The study should be powered to make inferences in subgroup analyses.

• Risk stratification methods should be used to control for selection bias. Data elements to be used in risk stratification models should include:

**Patient selection:**

• Patient Age at diagnosis of MDS and at transplantation

• Date of onset of MDS

• Disease classification (specific MDS subtype at diagnosis prior to preparative/conditioning regimen using World Health Organization (WHO) classifications). Include presence/absence of refractory cytopenias

• Comorbid conditions

• IPSS score (and WHO-adapted Prognostic Scoring System (WPSS) score, if applicable) at diagnosis and prior to transplantation

• Score immediately prior to transplantation and one year post-transplantation

• Disease assessment at diagnosis at start of preparative regimen and last assessment prior to preparative regimen Subtype of MDS (refractory anemia with or without blasts, degree of blasts, etc.)

• Type of preparative/conditioning regimen administered (myeloablative, non-myeloablative, reduced–intensity conditioning)

• Donor type

• Cell Source

• IPSS Score at diagnosis

Facilities must submit the required transplant essential data to the Stem Cell Therapeutics Outcomes Database

b. Nationally Non-Covered Indications

Effective for services performed on or after May 24, 1996, allogeneic HSCT is not covered as treatment for multiple myeloma.
2. Autologous Stem Cell Transplantation (AuSCT)

Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells.

a. Nationally Covered Indications

i. Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:
   - Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
   - Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
   - Recurrent or refractory neuroblastoma; or
   - Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

ii. Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
   - Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,
   - Adequate cardiac, renal, pulmonary, and hepatic function.

iii. Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
   - Amyloid deposition in 2 or fewer organs; and,
   - Cardiac left ventricular ejection fraction (EF) greater than 45%

b. Nationally Non-Covered Indications

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non primary AL amyloidosis; and,
- Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.
In these cases, AuSCT is not considered reasonable and necessary within the meaning of §1862(a)(1)(A) of the Act and is not covered under Medicare.

B. Other

All other indications for stem cell transplantation not otherwise noted above as covered or non-covered nationally remain at Medicare Administrative Contractor discretion.

**MEDICAID COVERAGE RATIONALE**

The following organ transplants, when deemed the principal form of treatment are covered:

a. Bone Marrow/Stem Cell – allogeneic and autologous;

b. Noncovered conditions for bone marrow/stem cell:
   1. Allogeneic stem cell transplantation is not covered as treatment for multiple myeloma;
   2. Autologous stem cell transplantation is not covered as treatment for acute leukemia not in remission, chronic granulocytic leukemia, solid tumors (other than neuroblastoma) and tandem transplantation for recipients with multiple myeloma;

A transplant procedure shall only be approved upon a determination that it is a medically necessary treatment by showing that:

a. The procedure is not experimental and/or investigational based on Title 42, Code of Federal Regulations (CFR), Chapter IV (Health Care Financing Administration) and Title 21, CFR, Chapter I FDA;

b. The procedure meets appropriate Medicare criteria;

c. The procedure is generally accepted by the professional medical community as an effective and proven treatment for the condition for which it is proposed, or there is authoritative evidence that attests to the proposed procedures safety and effectiveness; and

d. If the authorization request is for chemotherapy to be used as a preparatory therapy for transplants, an approval does not guarantee authorization for any harvesting or transplant that may be part of the treatment regimen. A separate authorization is required for Inpatient/outpatient harvesting or transplants, both in-state and out of state.

**REFERENCES**


Bensinger WI. (2) Reduced intensity allogeneic stem cell transplantation in multiple myeloma. Front Biosci. 2007 May;12:4384-4392.


Hematopoietic Stem Cell Transplant


Appendix

**AIDS-defining Conditions**

Certain serious and life-threatening diseases that occur in HIV-positive people are called "AIDS-defining" conditions. When a person gets one of these illnesses, he or she is diagnosed with the advanced stage of HIV infection known as AIDS.

The Centers for Disease Control and Prevention (CDC) has developed a list of these conditions (see below). No single patient is likely to have all of these problems. Some of the conditions are rare.

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, disseminated or extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary†
- Mycobacterium tuberculosis of any site, pulmonary,†§ disseminated,† or extrapulmonary†
- Mycobacterium, other species or unidentified species, disseminated† or extrapulmonary†
- Pneumocystis jiroveci pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month†
- Wasting syndrome attributed to HIV

* Only among children aged <13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged >13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)


Appendix

**Clinical, Cytogenetic and Mutational Risk Stratification for AML**

Favorable risk:
- Cytogenetics
  - t(8;21)
  - inv(16) or t(16;16)
- Mutations
  - Kit

Intermediate risk (one or more of the following):
- Cytogenetics
  - Normal
  - +8
- Mutations
  - Flt3 ITD-positive
  - Mutant TET2, MLL-PTD, DNMT3A, ASXL1, PHF6

Unfavorable (high) risk (one or more of the following):
- Cytogenetics
  - -5/-7
  - 11q23, 20q
  - 3 or more
- Clinical features:
  - CR2 and beyond
  - Age > 70
  - Refractory to induction chemotherapy
  - Persistence of minimal residual disease following induction

Appendix

The Dynamic International Prognostic Scoring System (DIPSS) for Primary Myelofibrosis (PMF)

The DIPSS for PMF uses five risk factors to predict survival. Values for score calculation are as follows:

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Point Value</th>
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<tbody>
<tr>
<td>Age &gt;65</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level &lt; 10 g/dl</td>
<td>2</td>
</tr>
<tr>
<td>White blood cell count (WBC) &gt; 25 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral blood blasts ≥ 1%</td>
<td>1</td>
</tr>
<tr>
<td>Presence of constitutional symptoms</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk categories: Low (score 0), intermediate-1 (score 1 or 2), intermediate-2 (score 3-4), high (score 5-6).


Appendix

Complete Remission and Partial Remission Highlights from Revised Response Criteria for Malignant Lymphoma (Cheson et al.)

Complete Remission (CR): Disappearance of all evidence of disease.

Nodal masses
- FDG-avid or PET positive prior to therapy: mass of any size permitted if PET negative
- Varibly FDG-avid or PET negative: regression to normal size on CT

Spleen, Liver
- Not palpable, nodules disappeared

Bone marrow
- Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

Partial Remission (PR): Regression of measurable disease and no new sites.

Nodal masses
- Greater than 50% decrease in sum of the products of diameters (SPD) of up to 6 largest dominant masses; no increase in size of other nodes

Hematopoietic Stem Cell Transplant
- FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site
- Variably FDG-avid or PET negative; regression on CT

NOTE: In the absence of adequate size measurements one can use a greater than 50% decrease in the Standardized Uptake Value (SUV) to document PR.

Spleen, Liver
- Greater than 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen.

Bone marrow
- Irrelevant if positive prior to therapy; cell type should be specified.


Appendix

**Hematopoietic Stem Cell Transplant Reference Sheet**

The following is a list of rare and unusual conditions where allogeneic transplant may be indicated. The list was reviewed and accepted by the 2016 Optum Hematopoietic Stem Cell Transplant Expert Panel. If there is a condition found on this list that is not included in the “Indications” section above, refer to Medical Director.

1. Lymphocyte Immunodeficiencies (many of these fall under ‘severe combined immunodeficiency’ classification)
   - Adenosine deaminase deficiency
   - Artemis deficiency
   - Calcium channel deficiency
   - Cernunnos-XLF immunodeficiency
   - CHARGE syndrome with immune deficiency
   - Common gamma chain deficiency
   - Deficiencies in CD4, CD3, CD8
   - DiGeorge syndrome
   - DNA ligase IV
   - Interleukin-7 receptor alpha deficiency
   - Janus-associated kinase 3 (JAK3) deficiency
   - Major histocompatibility class II deficiency
   - Purine nucleoside phosphorylase deficiency
   - Recombinase-activating gene (RAG) 1/2 deficiency
   - Reticular dysgenesis
   - Winged helix deficiency
   - Zeta-chain-associated protein-70 (ZAP-70) deficiency
2. Phagocytic Deficiencies
   - Chediak-Higashi syndrome
   - Griscelli syndrome, type 2
   - Interferon-gamma receptor deficiencies
   - Leukocyte adhesion deficiency
   - Shwachman-Diamond syndrome*
   *may be considered as marrow failure syndrome rather than immunodeficiency

3. Other Immunodeficiencies
   - Autoimmune lymphoproliferative syndrome
   - Cartilage hair hypoplasia
   - CD25 deficiency
   - Familial hemophagocytic lymphohistiocytosis
   - Hyper IgD and IgE syndromes
   - ICF syndrome
   - IPEX syndrome
   - NEMO deficiency
   - NF-κB inhibitor, alpha (IκB-alpha)


Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American


Appendix

Updated Criteria for Diagnosis of Multiple Myeloma (Rajkumar, 2014)

MULTIPLE MYELOMA
DIAGNOSTIC CRITERIA: ALL 3 REQUIRED

- Monoclonal plasma cells in the bone marrow > 10% and/or presence of a biopsy-proven plasmacytoma
- Monoclonal protein present in the serum and/or urine *
- Myeloma-related organ dysfunction (1 or more) **

Traditional CRAB Criteria:

[C] Calcium elevation in the blood S. Calcium >10.5 mg/l or upper limit of normal
[R] Renal insufficiency S. Creatinine > 2 mg/dl
[A] Anemia Hemoglobin < 10 g/dl or 2 g < normal
[B] Lytic bone lesions or osteoporosis *

NOTE: THESE CRITERIA IDENTIFY STAGE IB and STAGES II and III A/B MYELOMA BY DURIE/SALMON STAGE. Stage IA becomes smoldering or indolent myeloma.

* If no monoclonal protein is detected (non-secretory disease), then > 30 % monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

** The revised International Myeloma Working Group (IMWG) criteria will allow, in addition to the classic CRAB features, the following three markers as “myeloma defining events” (MDEs):

- Sixty percent or greater clonal plasma cells on bone marrow examination
- Serum involved/uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved free light chain is at least 100 mg/l (a patient’s “involved” free light chain – either kappa or lambda – is the one that is above the normal reference range; the uninvolved light chain is the one that typically is in, or below, the normal range)
- More than one focal lesion on MRI that is at least 5 mm or greater in size
The presence of at least one of these markers will be considered sufficient for a diagnosis of multiple myeloma, regardless of the presence or absence of symptoms or CRAB features. Each of these markers has been shown in two or more independent studies to be associated with an approximately 80% or higher risk of developing myeloma-related organ damage within two years.

In addition, the IMWG criteria allow the use of CT and PET-CT for detecting osteolytic bone lesions in order to make the diagnosis of myeloma. In patients with equivocal findings on MRI, CT, and/or PET-CT, the IMWG recommends follow-up imaging. The use of modern imaging methods at diagnosis and follow-up will enable the diagnosis of myeloma to be made before serious bone damage, such as pathologic fractures, can develop.

Appendix

**MGUS: MONOCLONAL GAMMOPATHY of UNDETERMINED SIGNIFICANCE**

**DIAGNOSTIC CRITERIA: ALL 3 REQUIRED**

- Serum monoclonal protein and/or urine monoclonal protein level low*  
- Monoclonal bone marrow plasma cells < 10%  
- Normal serum calcium, hemoglobin level and serum creatinine  
  * Low is defined as:  
    - Serum IgG < 3.5 g/dl  
    - Serum IgA < 2.0 g/dl  
- No bone lesions on full skeletal x-ray survey and/or other imaging if performed  
- No clinical or laboratory features of amyloidosis or light chain deposition disease  
- Urine monoclonal kappa or lambda < 1.0 g/24 hours  
- The definition of MGUS has not changed. However, a new entity termed light chain MGUS has been defined.

**SMOLDERING OR INDOLENT MYELOMA**

**DIAGNOSTIC CRITERIA: ALL 3 REQUIRED**

- Monoclonal protein present in the serum and/or urine  
- Monoclonal plasma cells present in the bone marrow and/or a tissue biopsy  
- Not meeting criteria for MGUS, multiple myeloma, or solitary plasmacytoma of bone

**NOTE: THESE CRITERIA IDENTIFY STAGE IA MYELOMA BY DURIE/SALMON STAGE.**

The diagnosis of smoldering myeloma will now have an upper limit of 60% for the percentage of clonal plasma cells in the marrow. Patients considered to have smoldering myeloma should not have any myeloma defining events or amyloidosis.

A new kind of smoldering multiple myeloma, termed light chain smoldering multiple myeloma, has been recently described in a study conducted at the Mayo Clinic, and the specific monoclonal protein level required for this diagnosis has also been added.

The foregoing Health Plan of Nevada/Sierra Health & Life Healthcare Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.

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