



TRANSPLANT REVIEW GUIDELINES

Hematopoietic Stem Cell Transplantation

Effective September 10, 2021

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Hematopoietic Stem Cell Transplant

Introduction

Hematopoietic stem cell transplants, including peripheral blood, bone marrow, and cord blood transplants are used most often to treat cancers affecting the blood or immune system. There are two main types of stem cell transplant: autologous and allogeneic. Autologous stem cells come from the person who will be receiving the transplant and are mainly used to treat leukemias, lymphomas, and multiple myeloma as well as other cancers such as testicular cancer and neuroblastoma. Autologous stem cell transplants are also used to treat certain childhood cancers. Allogeneic stem cells come from another individual. They can be from a matched related or unrelated donor or a donor without a complete match. Allogeneic stem cells are most commonly used to treat leukemias, lymphomas or non-malignant inherited disorders. An allogeneic transplant provides the advantage of a graft vs. cancer effect but occurs with the potential risk of graft vs. host disease. The need to balance these two outcomes makes this a more complicated procedure.

The purpose of this guideline is to identify the indications and contraindications for hematopoietic stem cell transplant as well as provide helpful reference tools to better understand a request for transplant.

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/or 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) $> 500 \mu\text{l}$ ($0.5 \times 10^9/\text{liter}$) after SCT, while secondary failure is associated with a successful SCT graft where neutrophils increase to $> 500 \mu\text{l}$ ($0.5 \times 10^9/\text{liter}$) 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 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 and other germ cell tumors, 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:
 - Single unit umbilical cord blood stem cell transplants are standard of care for children in many programs. Children who receive a single cord blood unit may experience prolonged time to engraftment and other post-transplant complications; therefore, a calculation of 2.5×10^7 nucleated cells per kilogram may improve response. (de Lima, 2006)
 - Umbilical cord blood and haploidentical donor cells are appropriate stem cell sources (Brunstein et al., 2007; Klingebiel et al., 2010) and can be used at the discretion of the treating team.
- 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)
- The definition of multiple myeloma has been updated. (Rajkumar et al., 2014) As such the diagnoses of frank myeloma, smoldering myeloma and MGUS have changed and can affect indications for treatment. (See Appendix.)

- To improve outcomes of blood and marrow transplantation, the use of maintenance therapy has become standard over the past few years. Maintenance therapy is considered an important component of the transplant event and therefore is covered if supported by adequate clinical evidence.
- 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
- Minimal/Measurable Residual Disease (MRD) is a measure of persistent disease which has emerged as a powerful tool in determining prognosis and informing treatment decisions for patients with hematologic malignancies. MRD detection is measured using flow cytometry, real-time quantitative polymerase chain reaction (RQ-PCR) or next-generation sequencing assays (Short, 2017). MRD is part of the standard evaluation of response to HSCT for several underlying disorders and is considered medically necessary.

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 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.

Disease/Indication	Auto	Allo	Comment
Leukemia			
<p>Acute Lymphoblastic Leukemia (ALL)</p> <p>McNeer et al., 2019</p>	✓	✓	<p>Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.</p> <p>The following cytogenetic features are associated with pediatric high-risk disease and may influence the decision to transplant in CR1:</p> <ul style="list-style-type: none"> • Hypodiploid ALL (< 44 chromosomes) • iAMP21
<p>Acute Myeloid Leukemia (AML)</p> <p>Dohner et al., 2017</p>	✓	✓	<p>Intermediate and high-risk AML including but not limited to:</p> <ul style="list-style-type: none"> • First complete response (CR1) with poor-risk cytogenetics or molecular markers • AML after relapse • CR2 and beyond <p>See Appendix for the definition of risk markers and clinical risk factors.</p> <p>Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.</p>
<p>Chronic Lymphocytic Leukemia (CLL)</p>	N	✓	<p>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.</p>

Disease/Indication	Auto	Allo	Comment
Chronic Myeloid Leukemia (CML)	N	✓	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.
Prolymphocytic Leukemia (Krishnan et al., 2010; Kalaycio et al., 2010)	✓	✓	
Myelodysplastic Syndromes & Mixed Myelodysplastic/Myeloproliferative Neoplasms			
Myelodysplastic Syndromes (MDS)	N	✓	
Juvenile Myelomonocytic Leukemia (JMML/JCML)	N	✓	
Chronic myelomonocytic leukemia (CMML) (Swerdlow et al.)	N	✓	The World Health Organization (WHO) classifies CMML as a myelodysplastic/myeloproliferative neoplasm.
Myeloproliferative Disorders			
Primary Myelofibrosis and related conditions (e.g. PRV)	N	✓	Allo approved with Intermediate-2 or High-Risk score using the Dynamic International Prognostic Scoring System Plus (DIPSS Plus). See Appendix for DIPSS Plus scoring system.
Secondary Myelofibrosis	N	✓	Allo transplant evaluation approved for patients with polycythemia vera or essential thrombocythemia.
Brain Tumors			
Anaplastic Astrocytoma	N		Not standard of care
Brain stem glioma	N		Not standard of care

Disease/Indication	Auto	Allo	Comment
Ependymoma	N		Not standard of care
Germinoma	N		Not standard of care
Glioblastoma Multiforme (GBM)	N		May be considered in infants
Medulloblastoma	✓		
Oligodendroglioma	✓		
Pineoblastoma	✓		
Embryonal Tumors with Multi-layered Rosettes (ETMR). Formerly known as Primitive Neuroectodermal Tumor (PNET)	✓		
Germ Cell Tumors			
Testicular Germ Cell Tumor	✓		Tandem auto can be approved
Extragonadal Germ Cell Tumor	✓		Tandem auto can be approved
Seminoma	✓		Tandem auto can be approved
Choriocarcinoma	✓		Tandem auto can be approved
Embryonal Carcinoma	✓		Tandem auto can be approved
Mixed Germ Cell Tumors	✓		Tandem auto can be approved
Teratoma	✓		Tandem auto can be approved
Yolk-Sac Tumor (Endodermal Sinus Tumor)	✓		Tandem auto can be approved

Disease/Indication	Auto	Allo	Comment
Germ Cell Tumor of the Ovary	✓		Tandem auto can be approved
Multiple Myeloma/ Plasma Cell Disorders			
Multiple Myeloma			Refer allograft request to Medical Director
a) Single auto	✓		
b) Tandem (auto followed by auto)	✓		
c) Tandem (auto followed by allo)	See SPECIAL CONSIDERATIONS		
d) Allogeneic	See SPECIAL CONSIDERATIONS		
AL-Amyloidosis	✓	N	
Waldenstrom Macroglobulinemia	✓	✓	
Monoclonal gammopathy of uncertain significance (MGUS)	N	N	No transplant indicated
POEMS (Polyneuropathy Organomegaly Endocrinopathy, Monoclonal Gammopathy Skin defects Syndrome) D'Souza et al., 2012; Ji et al., 2012; Li et al., 2013	✓	N	Autologous SCT may be appropriate. Refer to Medical Director.
Solitary Plasmacytoma	N	N	No transplant indicated
Hodgkin's Lymphoma			
Hodgkin's Lymphoma	✓	✓	

Disease/Indication	Auto	Allo	Comment
Non-Hodgkin's Lymphoma (NHL)			For autologous transplants, tumors must be chemosensitive which is defined as a complete or partial response based on the Cheson criteria. See Appendix for Cheson criteria.
Small B-cell lymphocytic lymphoma	N	✓	Auto not standard of care. This is treated in the same manner as CLL. Refer to Medical Director.
Follicular lymphoma Epperala et al., 2018; Oliansky et al., 2010; Sureda et al., 2018	✓	✓	
Lymphoplasmacytoid lymphoma/immunocytoma	✓	✓	
Marginal zone lymphoma (mucosa-associated lymphoid tissue, splenic, nodal)	✓	✓	
Burkitt lymphoma	✓	✓	
Diffuse, large cell lymphoma (mediastinal large cell, primary effusion) Oliansky et al. 2011	✓	✓	
Mantle cell lymphoma	✓	✓	
Precursor B-cell leukemia/lymphoma	✓	✓	
T-cell Lymphoma	✓	✓	
Other Malignancies			
Atypical Teratoid Rhabdoid Tumors Nikolaides et al., 2010	✓	N	Tandem auto may be indicated. May be appropriate as part of a clinical trial.

Disease/Indication	Auto	Allo	Comment
Blastic Plasmacytoid Dendritic Cell Neoplasm Dietrich et al., 2014	N	✓	
Epithelial Ovarian Cancer	N	N	Not standard of care
Ewing Tumor (Ewing Sarcoma)	✓	N	Allogeneic not standard of care
Neuroblastoma	✓	N	Tandem auto can be approved
Osteogenic sarcoma	N	N	Not standard of care
Renal Cell Carcinoma	N	N	Not standard of care
Retinoblastoma	✓	N	Allogeneic not standard of care
Rhabdomyosarcoma/soft tissue sarcoma Stiff et al., 2010	N	N	May be appropriate as part of a clinical trial. Refer to Medical Director
Supratentorial ependymoma Venkatramani et al., 2013	✓		
Wilms Tumor Brown et al.,2010; Campbell et al., 2004	✓	N	May be appropriate in relapsed disease as part of a clinical trial. Refer to Medical Director
Hematological Disorders			
Aplastic Anemia		✓	
Blackfan-Diamond Syndrome		✓	
Chronic Granulomatous Disease		✓	
Congenital Agranulocytosis (Kostmann Syndrome)		✓	

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Disease/Indication	Auto	Allo	Comment
Congenital Amegakaryocytic Thrombocytopenia		✓	
Dyskeratosis Congenita		✓	
Fanconi Anemia		✓	
Paroxysmal Nocturnal Hemoglobinuria (PNH)		✓	
Shwachman-Diamond Syndrome		✓	
Sickle Cell Disease		✓	
Thalassemia Major		✓	
Immunodeficiency Syndromes			
CD40 Ligand Deficiency		✓	
Chediak-Higashi Syndrome		✓	
Hemophagocytic Lymphohistiocytosis (HLH) (same as Familial Erythrophagocytic Lymphohistiocytosis - FEL)		✓	
Leukocyte Adhesion Deficiency		✓	
Omenn Syndrome		✓	

Disease/Indication	Auto	Allo	Comment
Severe Combined Immunodeficiency Disease (SCID)*		✓	<p>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.</p> <p>*As new genetic abnormalities are identified that can result in immunodeficiency syndromes, allogeneic transplantation may be appropriate treatment.</p>
Wiskott-Aldrich Syndrome		✓	
X-linked Lymphoproliferative Syndrome		✓	
Gaucher disease type I Pastores et al., 2004; Charrow et al.,2004; Peters & Steward, 2003; Jmoudiak & Futerman, 2005		✓	Patients with the non-neuropathic type may benefit from a stem cell transplant following failed enzyme replacement therapy or if significant bone pain exists despite enzyme replacement therapy.
Niemann-Pick type B Schuchman, 2009		✓	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.
Fucosidosis Miano et al.,2001; Vellodi et al., 1995		✓	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.

Disease/Indication	Auto	Allo	Comment
Lysosomal storage diseases Heese, 2008		✓	
Autoimmune Diseases			
Crohn's Disease	N	N	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.
Multiple Sclerosis (Cohen et al., 2019; Hooper, 2011; Kurtzke, 1982; National Multiple Sclerosis Society, 2011)	Y	N	<ul style="list-style-type: none"> • Patient must meet the definition of relapsing-remitting* (RR) or secondary progressive* (SP) multiple sclerosis • Expanded Disability Status Scale (EDSS) score between 2.0 and 6.0 • Patient has failed treatment with one or more disease-modifying therapies (DMT) • Evidence of either of the following while being treated with DMT: <ul style="list-style-type: none"> -two or more clinical relapses* at separate times but within the previous 12 months - one relapse* and a magnetic resonance imaging (MRI) gadolinium-enhancing lesion(s) at a separate time than the relapse but within the previous 12 months <p>See Appendix for definitions of Relapsing-Remitting MS (RRMS), Secondary-Progressive MS (SPMS), and relapse of MS.</p>
Rheumatoid Arthritis	N	N	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.

Disease/Indication	Auto	Allo	Comment
Systemic lupus erythematosus (SLE)	N	N	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.
Systemic Sclerosis (Scleroderma) Host et al., 2017; Sullivan et al., 2019	Y	N	Adult patients at least 18 years of age with rapidly progressive systemic sclerosis (scleroderma) scleroderma (systemic sclerosis) at risk of organ failure with either: <ul style="list-style-type: none"> • Pulmonary involvement with active interstitial lung disease and both: <ul style="list-style-type: none"> ○ Consistent bronchoalveolar cell composition or ground-glass opacities on CT of the chest ○ Either a forced vital capacity (FVC) or a diffusing capacity of the lung carbon monoxide (DLco) of less than 70% of the predicted value. • Renal involvement • Patient does not have ANY of the following: <ul style="list-style-type: none"> ○ a DLco of less than 40% of predicted value ○ an FVC of less than 45% of predicted value ○ a creatinine clearance of less than 40 ml per minute ○ pulmonary arterial hypertension, ○ a left ventricular ejection fraction of less than 50% • Patient is felt to be an appropriate candidate for autologous transplant by the treating facility
Inherited Metabolic Disorders			
Adrenoleukodystrophy		✓	

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Disease/Indication	Auto	Allo	Comment
Epidermolysis Bullosa		✓	
Globoid Cell Leukodystrophy (Krabbe Disease)		✓	
Hurler Syndrome (MPS I)		✓	
Hunter Syndrome (MPS II)		✓	
Mannosidosis		✓	
Maroteaux-Lamy Syndrome (MPS VI)		✓	
Metachromatic Leukodystrophy		✓	
(MNGIE) Mitochondrial Neurogastrointestinal Encephalopathy (Halter et al., Filosto et al.)		✓	
Osteopetrosis		✓	
Rett Syndrome		✓	
Cardiac Conditions			
Heart Disease	N	N	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.
Additional Condition/Disease Indications			

Disease/Indication	Auto	Allo	Comment
Refer to section titled: Hematopoietic Stem Cell Transplant Reference Sheet in the Appendix		✓	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.

Relative Contraindications

NOTE: The following list contains potential contraindications for hematopoietic stem cell transplant. While the conditions listed below would not be absolute contraindications for treatment they need to be addressed prior to transplant.

- Infections
 - Systemic or uncontrolled infection including sepsis.
- Significant uncorrectable life-limiting medical conditions.
- Severe end stage organ damage that would have an impact on patient survival.
- 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.
- Limited irreversible rehabilitative potential (Bunnapradist, 2007).

Special Considerations

Additional consultation and/or evaluation may be indicated in these situations. Refer to Medical Director if questions remain.

- 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 preceded 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) if 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)
- HIV infection
 - Patients should have a formal infectious disease consult indicating adequate treatment and proper assessment of risks related to this transplant.

- 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 (\leq 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.
- Active untreated or untreatable malignancy in patients undergoing stem cell transplantation for non-malignant indications
 - Refer to Medical Director
- Patients with post-transplant lymphoproliferative disease (PTLD), having failed other conventional therapies, must have no active disease as demonstrated by negative positron emission tomography (PET) scan and resolved adenopathy on computed tomography (CT) and/or magnetic resonance imaging (MRI) (Blaes, 2009; Khedmat, 2009, Panagiotidis, 2014).
- Patients with human immunodeficiency virus (HIV) infection must be on a HAART regimen and there must be documented evidence of viral load suppression.

Hematopoietic Stem Cell Transplant — Timing for Stem Cell Transplant Consultation

RECOMMENDED TIMING FOR STEM CELL TRANSPLANTATION CONSULTATION (National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation)

<https://bethematchclinical.org/transplant-indications-and-outcomes/additional-outcomes/timing-impact-on-outcomes/>

These guidelines for transplant consultation were developed jointly and updated in 2019 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 MYELOYDYSPLASIA

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) without c-*KIT* mutation; t (15;17); normal cytogenetics with NPM1 or isolated biallelic CEBPA mutation and without FLT3-ITD)
 - Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))
 - Treatment-related leukemia
 - First relapse
 - Primary induction failure
 - Presence of minimal residual disease after initial 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
 - Presence of minimal residual disease after initial therapy
 - CR2 and beyond, if not previously evaluated
 - First relapse

Myelodysplastic Syndromes (MDS)

- Any intermediate or high IPSS score
- Any MDS with poor prognostic features, including:
 - Treatment-related MDS
 - Refractory cytopenias
 - Adverse cytogenetics and molecular features
 - Transfusion dependence
 - Failure of hypomethylating agents or chemotherapy
 - Moderate to severe marrow fibrosis

Chronic Myelogenous Leukemia (CML)

- Inadequate hematologic or cytogenetic/molecular response to tyrosine kinase inhibitor (TKI) therapies
- Disease progression
- Intolerance to TKI therapies
- Accelerated phase
- Blast crisis (myeloid or lymphoid)

Chronic Lymphocytic Leukemia (CLL)

- Richter's transformation
- Second or greater relapse following chemoimmunotherapy

Myelofibrosis

- DIPSS Intermediate-2 (INT-2) and high-risk disease
- DIPSS Intermediate-1 (INT-1) with low platelet counts, red blood cell transfusion dependent, complex cytogenetics
- High-risk driver mutations (*ASXL1*, *EZH2*, *TET2*, *IDH1*, *IDH2*, *SRSF2*, and *TP53*) or triple negative (lack of a driver mutation such as *JAK2*, *MPL*, or *CALR*) should be considered in decision-making.

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 *NPM1* or isolated biallelic *CEBPA* mutation and without FLT3-ITD]
 - Primary induction failure
 - Monosomy 5 or 7
 - Age <2 years at diagnosis
 - Treatment-related leukemia
 - Presence of minimal residual disease after initial therapy
 - CR2 and beyond, if not previously evaluated
 - First relapse

Acute Lymphoblastic Leukemia (ALL) (age < 15 years)

- Infant at diagnosis
- High/very high-risk CR1 including:
 - Philadelphia chromosome positive slow-TKI responders or with *IKZF1* deletions; Philadelphia-like
 - 11q23 rearrangement
 - iAMP21
- Primary induction failure
- Presence of minimal residual disease after initial therapy
- CR2 and beyond, if not previously evaluated
- First relapse

Acute Lymphoblastic Leukemia (ALL) (adolescent and young adults age 15-39 years)

- Primary induction failure
- Presence of minimal residual disease after initial therapy
- High/very high-risk CR1 including:
 - Philadelphia chromosome positive or Philadelphia-like
 - iAMP21
 - 11q23 rearrangement
 - B-cell with poor-risk cytogenetics
- First relapse
- CR2 and beyond, if not previously evaluated

Myelodysplastic Syndromes (MDS)

- At diagnosis for all subtypes

Juvenile Myelomonocytic Leukemia (JMML)

- At diagnosis

LYMPHOMAS

Non-Hodgkin Lymphoma

- Follicular
 - Poor response to initial treatment
 - Initial remission duration <24 months
 - First relapse
 - Transformation to diffuse large B-cell lymphoma

Diffuse Large B-Cell

- At first relapse
- CR2 or subsequent remission
- Primary induction failure, including residual PET avid disease
- Double or triple hit (*MYC* and *BCL-2* and/or *BCL-6*) – at diagnosis
- Primary CNS lymphoma at diagnosis

High Grade Lymphoma

- *C-myc* rearrangement at diagnosis
- Primary induction failure
- CR1
- First relapse
- CR2 or subsequent remission

Mantle Cell

- At diagnosis
- First relapse
- Bruton's tyrosine kinase (BTK) intolerant or resistant disease

Mature T-cell

- CR1
- First relapse

Other High-Risk Lymphomas

- At diagnosis

Hodgkin Lymphoma

- Primary induction failure
- **CR2** or subsequent remission
- First relapse

Multiple Myeloma

- All patients after initiation of therapy
- At diagnosis
- At first progression

OTHER MALIGNANT DISEASES

Germ cell tumors

- Short initial remission
- Poor initial response

Neuroblastoma

- INSS stage 2 or 3 at diagnosis
 - *MYCN* amplification (>4x above reference)
- INSS stage 4 at diagnosis
 - *MYCN* amplification (>4x above reference)
 - Age > 18 months at diagnosis
 - Age 12-18 months with unfavorable characteristics
- Metastatic disease at diagnosis
- Progressive disease while on therapy or relapsed disease

Ewing Family of Tumors

- Metastatic disease at diagnosis
- First relapse or CR2

NON-MALIGNANT DISORDERS

Immune Deficiency Diseases (including severe combined immunodeficiency syndromes, Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, Kostmann syndrome, severe neutropenia and others)

- At diagnosis or if detected on newborn screening

Inherited Metabolic Disorders (including Hurler syndrome, adrenoleukodystrophy, and others)

- At diagnosis or if detected on newborn screening

HEMAGLOBINOPATHIES

Transfusion-Dependent Thalassemias

- At diagnosis

Sickle Cell Disease

- Children with available matched sibling donor
- All patients with aggressive course (stroke, 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

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Hematopoietic Stem Cell Transplant

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Appendix

Multiple Sclerosis Definitions

Relapsing-Remitting MS (RRMS)

A pattern of symptoms of multiple sclerosis in which symptomatic attacks occur that last 24 hours or more., followed by complete or almost complete improvement. This is the most common form of multiple sclerosis. About 85% of people with MS are initially diagnosed with RRMS. People with RRMS have temporary periods called relapses, flare-up or exacerbations, when new symptoms appear. (Hooper, 2011)

Secondary-Progressive MS (SPMS)

A pattern of symptoms of multiple sclerosis in which there are relapses and remissions, followed by more steady progression of symptoms. In SPMS, symptoms worsen more steadily over time, with or without the occurrence of relapses and remissions. Most people who are diagnosed with RRMS will transition to SPMS at some point. (National Multiple Sclerosis Society, 2011)

Relapse

A relapse of MS (also known as also known as an exacerbation attack or flare-up) is the occurrence new symptoms or the worsening of old symptoms. It can be very mild, or severe enough to interfere with a person's ability to function. No two exacerbations are alike. Symptoms vary from person to person and from one exacerbation to another. For example, the exacerbation might be an episode of optic neuritis (caused by inflammation of the optic nerve that impairs vision), or problems with balance or severe fatigue. Some relapses produce only one symptom (related to inflammation in a single area of the central nervous system). Other relapses cause two or more symptoms at the same time (related to inflammation in more than one area of the central nervous system).

To be a true exacerbation, the attack must last at least 24 hours and be separated from the previous attack by at least 30 days. It must also occur in the absence of infection, or other cause. Most exacerbations last from a few days to several weeks or even months. (National Multiple Sclerosis Society, 2011)

Hooper K. Managing Progressive MS. New York, NY: National Multiple Sclerosis Society; 2011. Gale Encyclopedia of Medicine. Copyright 2008 The Gale Group, Inc. All rights reserved.

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Multiple Sclerosis: Just the Facts New York, NY; National Multiple Sclerosis Society;2011 Gale Encyclopedia of Medicine. Copyright 2008 The Gale Group, Inc. All rights reserved.

<https://www.nationalmssociety.org/Treating-MS/Managing-Relapses>

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

Patel JP, Levine RL. How do novel molecular genetic markers influence treatment decisions in acute myeloid leukemia? *Hematology Am Soc Hematol Educ Program*. 2012; 2012:28-34.

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

DIPSS Factors	Point Value
Age > 65	1
Hemoglobin level < 10 g/dl	2
White blood cell count (WBC) > 25 x 10 ⁹ /L	1
Peripheral blood blasts ≥ 1%	1
Presence of constitutional symptoms	1

DIPSS Risk Categories: Low (0 points), Intermediate 1 (1 point), Intermediate 2 (2-3 points), High (≥ 4 points).

DIPSS-Plus Factors	Point Value
Adverse karyotypes*	1
Platelets < 100 x 10 ⁹ /L	1
RBC transfusion need	1

*Adverse karyotypes include +8, -5/del5q, -7/del7q(17q), inv(3), 11q23 rearrangements.

DIPSS-Plus Risk Categories: Low (0 points), Intermediate 1 (1 point), Intermediate 2 (2-3 points), High (4-6 points).

Five parameters are scored in the DIPSS. Three additional factors are added in the DIPSS-Plus. The final score in the DIPSS-Plus is composed of the value assigned in the DIPSS risk categories plus the points added from the three DIPSS-Plus factors (Gangat et al.).

Gangat N, Caramazza D, Vaidya R. et al. DIPSS Plus: A refined dynamic international prognostic scoring system for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011;29(4):392-97.

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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
- Variably 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
 - 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.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579–86. Available at: <http://jco.ascopubs.org/content/25/5/579.full.pdf+html>.

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 2018 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 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 CD 45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV
- DOCK8 immunodeficiency syndrome
- GATA2 deficiency
- 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- κ B inhibitor, alpha (I κ B-alpha)

Antoine C, Muller S, Cant A, et al. Long term survival and transplantation of hematopoietic stem cells for immunodeficiencies: report of the European experience 1968-99. *Lancet*. 2003 Feb;361(9357):553-60. PMID: 12598139254.

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Appendix

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Updated Criteria for Diagnosis of Multiple Myeloma

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.

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.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15: e538-48.

The following are approved changes incorporated into the revision numbers indicated below.	
Revision	Date, Description of Change, and Name
1.0	07/19/2012: New guideline. Approved by Medical Technology Assessment Committee
1.0	08/14/2012: Approved by National Medical Care Management Committee
2.0	10/10/13: Revised and updated. Approved by Medical Technology Assessment Committee
2.0	10/16/2013: Approved by Complex Medical Conditions Policy Committee
2.0	11/12/13: Approved by the National Medical Care Management Committee
3.0	08/07/2014: Approved by Medical Technology Assessment Committee
3.0	09/09/2014: Approved by National Medical Care Management Committee
4.0	8/25/2015: Annual review; revised and updated
4.0	09/03/2015: Approved by Medical Technology Assessment Committee
4.0	10/13/2015: Approved by National Medical Care Management Committee
5.0	08/15/2016: Annual review. Revised and updated. Transplant Review Guidelines separated into two documents: Hematopoietic Stem Cell Transplantation and Solid Organ Transplantation.
5.0	09/01/2016: Approved by Medical Technology Assessment Committee
5.0	09/13/2016: Approved by National Medical Care Management Committee

Appendix

6.0	6/22/2017: Approved by Optum Policy and Guideline Committee
6.0	07/06/2017: Approved by Medical Technology Assessment Committee
6.0	07/11/2017: Approved by National Medical Care Management Committee
7.0	09/07/2017: New content relevant to CAR-T Therapy approved by Medical Technology Assessment Committee.
7.0	09/12/2017: New content relevant to CAR-T Therapy approved by National Medical Care Management Committee.
7.0	11/1/2017: Updated to reflect FDA-approval of new CAR-T Therapy agent axicabtagene ciloleucel (<i>Yescarta</i> [™] , Kite Pharma).
8.0	11/13/2017: Corrected CAR-T prior authorization statement on page 7.
9.0	08/02/2018: Approved by Medical Technology Assessment Committee
9.0	09/11/2018: Approved by National Medical Care Management Committee
10.0	4/17/2019: Annual review with Optum Stem Cell Expert Panel. Minor revisions including addition of CMML to approved indications for allogeneic stem cell transplant; revised the preferred scoring system for primary myelofibrosis; revised systemic sclerosis indication to approve autologous transplant; added allogeneic transplant evaluation for secondary myelofibrosis in patients with polycythemia vera and essential thrombocytopenia; and added DIPSS-Plus factors table and scoring directions. Updated references.
10.0	06/06/2019: Approved by Medical Technology Assessment Committee
10.0	06/11/2019: Approved by National Medical Care Management Committee
11.0	12/2/2019: Corrected follicular lymphoma indication on page 10. Updated supporting references.

Appendix

12.0	6/10/2020: Annual review with Optum Stem Cell Expert Panel. Revisions to the MRD statement, Relative Contraindications and Special Considerations sections, and NMDP recommendations for timing of transplant consultation. References updated throughout.
12.0	8/6/2020: Approved by Medical Technology Assessment Committee
12.0	8/11/2020: Presented to National Medical Care Management Committee 11/11/20: Updated minimal/measurable disease terminology.
13.0	6/15/21: Annual Review with Optum Stem Cell Expert Panel. No revisions.
13.0	9/9/21: Approved by Medical Technology Assessment Committee
13.0	9/14/21: Presented to National Medical Care Management Committee



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