



Hematopoietic Stem Cell Transplantation

Clinical guidelines

For Ohio Only

Effective Date: 01/01/2024

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Application

This clinical guideline applies only to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using [Ohio Administrative Code 5160-1-01](#).

In accordance with Ohio Administrative Code 5160-2-65 (L), reimbursement for bone marrow transplant and hematopoietic stem cell transplant is contingent upon review and the recommendation by the [Ohio Hematopoietic Transplant and Cellular Therapy Consortium | Galena, OH | Cause IQ](#) based on criteria established by Ohio experts in the field of bone marrow transplant and authorization from the department. Reimbursement is further contingent upon:

- (a) Membership in the “Ohio Hematopoietic Stem Cell Transplant Consortium”; or
- (b) Compliance with the performance standards described in agency 3701 of the Administrative Code, and the performance of ten autologous or ten allogeneic bone marrow transplants, dependent on which volume criteria is appropriate for the transplant requested.

For harvesting costs for bone marrow transplant services, the prospective payment amount will be either:

- (a) The DRG amount as described in this rule if the donor is a Medicaid recipient or if the bone marrow transplant is autologous
- (b) The product of the covered billed charges times the hospital-specific, Medicaid inpatient cost-to-charge ratio as described in [Rule 5160-2-22 - Ohio Administrative Code | Ohio Laws](#), if the donor is not a Medicaid recipient.” ([Rule 5160-2-65 - Ohio Administrative Code | Ohio Laws](#))

Prior authorization activities must be conducted in accordance with the Ohio Department of Medicaid Managed Care Provider Agreements located at: [Managed Care Agreements \(ohio.gov\)](#).

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.
- While the development of chimeric antigen receptor T-cell (CAR T) therapy has introduced a new field of therapeutic possibilities for patients with certain hematological malignancies, hematopoietic stem cell transplantation remains a cornerstone of care.
- 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. There is not a standardized approach to the use of DLI and can come at various times following the initial transplant (Castagna et al., 2016).
 - Requests for DLI should be referred to the medical director.
- 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 μ l (0.5×10^9 /liter) after SCT, while secondary failure is associated with a successful SCT graft where neutrophils increase to > 500 μ l (0.5×10^9 /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 et al., 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 & Moreau, 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 et al., 2013).
- 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.
- Delayed engraftment is a significant limitation of umbilical cord blood transplantation (UCBT) due in part to low cell doses and a defect in the cord blood cells' ability to home to the bone marrow (Popat et al., 2015). In April 2023, the FDA approved Omidubicel only (Omisirge®) for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce time to neutrophil engraftment and the incidence of infection. Omidubicel is an ex vivo expanded hematopoietic progenitor cell and nonexpanded myeloid and lymphoid cell product derived from a single umbilical cord blood unit. Horwitz et al. (2021) reported the outcomes of a phase 3 trial evaluating the efficacy of Omidubicel vs standard UCBT in 125 patients aged 13 to 65 years with hematologic malignancies. Patients were randomly assigned to Omidubicel or standard UCBT. All patients received myeloablative conditioning and prophylaxis with a calcineurin inhibitor and mycophenolate mofetil for graft-versus-host disease (GVHD). The primary endpoint was time to neutrophil engraftment. In the Omidubicel arm, median time to neutrophil engraftment was 12 days (95% CI, 10-14 days) and 22 days (95% CI, 19-25 days) for the control arm. The cumulative incidence of engraftment was 96% for patients receiving Omidubicel and 89% for patients receiving standard UCBT. Additionally, the Omidubicel arm experienced faster platelet recovery (55% vs 35% recovery by 42 days; $P = .028$), had lower incidence of first grade 2 to 3 bacterial or invasive fungal infection (37% vs 57%; $P = .027$) and spent more time out of the hospital during the first 100 days after transplant (median, 61 vs 48 days; $P = .005$) than controls. Of note, the logistical complexity of producing Omidubicel led to a median 2-week delay in time from randomization to transplantation. The authors report this delay did not result in increased risk of pretransplant relapse in the 52 patients transplanted with Omidubicel. It should also be noted that Lin et al. (2023) reported donor-derived myeloid neoplasm were an adverse event of special interest. Donor-derived myelodysplastic syndrome (MDS) occurred in one patient receiving Omidubicel in the fourth year post-transplant while two patients developed post-transplant lymphoproliferative disorder (PTLD) in the second year post-transplant.
- Omidubicel only may be considered medically necessary to reduce time to neutrophil recovery and incidence of infection when all of the following are met:
 - Patient is 12 years of age or older
 - Has been diagnosed with a hematologic malignancy
 - Is a candidate for myeloablative allogeneic HSCT
 - Has no readily available matched sibling or matched unrelated donor
 - Is expected to require more than one cord blood unit
 - Following a comprehensive evaluation of the clinical condition it is felt this is the best choice of cell source for this particular patient
- 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

Medical necessity determinations must comply with the definitions and principles established in [Rule 5160-1-01 - Ohio Administrative Code | Ohio Laws](#).

Hematopoietic stem cell transplantation is considered medically necessary in certain indications. The Ohio Department of Medicaid recognizes the use of InterQual® criteria secondary to the decision of the Ohio Hematopoietic Transplant and Cellular Therapy Consortium. For medical necessity clinical coverage criteria, refer to the InterQual® CP: Procedures, Transplantation, Allogeneic Stem Cell, Transplantation, Allogeneic Stem Cell (Pediatric), Transplantation, Autologous Stem Cell, and Transplantation, Autologous Stem Cell (Pediatric).

View the InterQual® criteria at: [InterQual® \(cue4.com\)](https://www.cue4.com)

When reviewing the table on the following pages:

- ✓ = Medically necessary
- N = Not medically necessary
- 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.

| Disease/Indication | Auto | Allo | Comment |
|---|------|------|---|
| Leukemia | | | |
| Acute Lymphoblastic Leukemia (ALL) McNeer et al., 2019 | ✓ | ✓ | Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director. The following cytogenetic features are associated with pediatric high-risk disease and may influence the decision to transplant in CR1: <ul style="list-style-type: none"> • Hypodiploid ALL (< 44 chromosomes) • iAMP21 |

| Disease/Indication | Auto | Allo | Comment |
|---|-------------|-------------|---|
| Acute Myeloid Leukemia (AML) Dohner et al., 2017 | ✓ | ✓ | Intermediate and high-risk AML including but not limited to: <ul style="list-style-type: none"> • First complete response (CR1) with poor-risk cytogenetics or molecular markers • AML after relapse • CR2 and beyond See Appendix for the definition of risk markers and clinical risk factors. Autologous SCT may be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director. |
| Chronic Lymphocytic Leukemia (CLL) | N | ✓ | 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. |
| 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 Kalaycio et al., 2010; Krishnan 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., 2017 | N | ✓ | The World Health Organization (WHO) classifies CMML as a myelodysplastic/myeloproliferative neoplasm. |
| Myeloproliferative Disorders | | | |

| Disease/Indication | Auto | Allo | Comment |
|---|-------------|-------------|---|
| Primary Myelofibrosis and related conditions (e.g., PRV) Gagelman et al., 2019 | 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. The identification of adverse karyotypes is evolving. New clinical-molecular scoring systems may be useful in determining post-transplant prognosis. |
| 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 |
| 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 |
| Germ Cell Tumor of the Ovary | ✓ | | Tandem auto can be approved |

| Disease/Indication | Auto | Allo | Comment |
|---|-----------------------------|------|--|
| 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 | Allogeneic SCT may be appropriate on clinical trial. |
| Waldenstrom Macroglobulinemia | ✓ | ✓ | |
| Monoclonal gammopathy of renal significance (MGRS) | See SPECIAL CONSIDERATIONS. | | |
| 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 | ✓ | ✓ | |
| 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 | ✓ | ✓ | |

| Disease/Indication | Auto | Allo | Comment |
|---|-------------|-------------|---|
| 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. |
| 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 | | ✓ | |

| Disease/Indication | Auto | Allo | Comment |
|---|------|------|---|
| Congenital Agranulocytosis (Kostmann Syndrome) | | ✓ | |
| Congenital Amegakaryocytic Thrombocytopenia | | ✓ | |
| Dyskeratosis Congenita | | ✓ | |
| Fanconi Anemia | | ✓ | |
| Paroxysmal Nocturnal Hemoglobinuria (PNH) | | ✓ | |
| Shwachman-Diamond Syndrome | | ✓ | |
| Sickle Cell Disease (SCD) | | ✓ | American Society of Hematology (ASH) has published a guideline consisting of eight recommendations for HSCT for SCD (Kanter et al., 2021). Available at: American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation Blood Advances American Society of Hematology (ashpublications.org) |
| Thalassemia Major | | ✓ | |
| Immunodeficiency Syndromes | | | |
| CD40 Ligand Deficiency | | ✓ | |
| Chediak-Higashi Syndrome | | ✓ | |
| Hemophagocytic Lymphohistiocytosis (HLH) (same as Familial Erythrophagocytic Lymphohistiocytosis - FEL) | | ✓ | |
| Leukocyte Adhesion Deficiency | | ✓ | |
| Omenn Syndrome | | ✓ | |
| Severe Combined Immunodeficiency Disease (SCID)* | | ✓ | 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. *As new genetic abnormalities are identified that can result in immunodeficiency syndromes, allogeneic transplantation may be appropriate treatment. |
| Wiskott-Aldrich Syndrome | | ✓ | |

| Disease/Indication | Auto | Allo | Comment |
|--|-------------|-------------|---|
| 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. |
| 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. |

| Disease/Indication | Auto | Allo | Comment |
|---|------|------|---|
| <p>Multiple Sclerosis</p> <p>Cohen et al., 2019; Hooper, 2011; Kurtzke, 1982; National Multiple Sclerosis Society, 2011</p> | 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. |
| 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. |

| Disease/Indication | Auto | Allo | Comment |
|--|------|------|---|
| <p>Systemic Sclerosis (Scleroderma)</p> <p>Host et al., 2017; Sullivan et al., 2018</p> | Y | N | <p>Adult patients at least 18 years of age with rapidly progressive systemic sclerosis (scleroderma) scleroderma (systemic sclerosis) at risk of organ failure with either:</p> <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 | | ✓ | |
| Epidermolysis Bullosa | | ✓ | |
| Globoid Cell Leukodystrophy (Krabbe Disease) | | ✓ | |
| Hurler Syndrome (MPS I) | | ✓ | |
| Hunter Syndrome (MPS II) | | ✓ | |
| Mannosidosis | | ✓ | |
| Maroteaux-Lamy Syndrome (MPS VI) | | ✓ | |
| Metachromatic Leukodystrophy | | ✓ | |
| <p>Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE)</p> <p>Filosto et al., 2012 Halter et al., 2011;</p> | | ✓ | |

| Disease/Indication | Auto | Allo | Comment |
|---|------|------|---|
| 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 | | | |
| Refer to section titled: Hematopoietic Stem Cell Transplant Reference Sheet in the AppendixError! Reference source not found. | | ✓ | 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

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 hypodiploidy 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)

- Monoclonal gammopathy of renal significance (MGRS) is a clonal proliferative disorder that produces a nephrotoxic monoclonal immunoglobulin and does not meet previously defined hematological criteria for treatment of a specific malignancy. Monoclonal immunoglobulin-related diseases show higher rates of recurrence after kidney transplantation (often > 80%) than their non-monoclonal counterparts. They are poorly responsive to conventional immunosuppression (Leung et al., 2019). Targeting the underlying B-cell clone with chemotherapy, although it is not an evidently malignant clone per se, is the only available treatment option for MGRS. High-dose melphalan (HDM) supported by autologous SCT may be a therapeutic option in some patients (Ferland et al., 2013). Refer requests for SCT in patients with MGRS to Medical Director.
 - Autologous SCT may be appropriate in patients with MGRS who meet the following:
 - Have failed chemotherapy targeting the underlying B-cell clone
 - AND
 - Have sufficient renal function to tolerate high-dose chemotherapy Initial therapy in newly diagnosed patients with high-risk disease and in otherwise good health
- HIV infection
 - Patients should have a formal infectious disease consult indicating adequate treatment and proper assessment of risks related to this transplant.
 - Patients with known HIV infection must be on a HAART regimen and there must be documented evidence of viral load suppression.
- Refer to requesting program patient selection criteria for age-specific criteria
 - If outside program's patient selection criteria, refer to Medical Director
- Serum creatinine < 2.5 mg/dL (\leq 1.5 mg/dL in children) or GFR > 50ml/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).

Hematopoietic Stem Cell Transplant — Timing for Stem Cell Transplant Consultation

These 2022 guidelines were developed jointly by the National Marrow Donor Program® (NMDP®)/Be the Match® and the American Society for Transplant and Cellular Therapy (ASTCT), and are based on current clinical practice, medical literature, National Comprehensive Cancer Network® (NCCN®) Guidelines for the treatment of cancer and evidence-based reviews.

The guidelines identify appropriate timing of consultation for autologous or allogeneic hematopoietic cell transplantation (HCT) based on disease characteristics. Evaluation and coordination of timing of HCT for eligible patients is determined in collaboration with the transplant center. Early referral is a critical factor for optimal transplant outcomes. In many situations, there may be a narrow window of opportunity to proceed to transplant and delays might preclude transplant or impair transplant outcomes. Research data comparing outcomes by disease status can be found at [Referral Timing Guidelines](#). [Referral Timing Guidelines \(bethematchclinical.org\)](#).

Adult leukemias and myelodysplasia

Acute Myeloid Leukemia (AML)

- High-resolution HLA typing is recommended at diagnosis for all patients
- HCT consultation should take place early after initial diagnosis for all patient with AML, including:
 - Primary induction failure
 - Measurable (also known as minimal) residual disease after initial therapy
 - CR1- except favorable risk AML [defined as: *t(8:2109q22;q22.1)*; *RUNX1-RUNX1T1*, *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22)*; *CBFB-MYH11*, mutated *NPM1* without *FLT3-ITD*, biallelic mutated]. Early referral for allogeneic HCT should also be considered for any AML patients in CR1 who are 60 years or older; regardless of cytogenetic or genomic information.
 - Antecedent hematological disease (e.g., myelodysplastic syndrome [MDS])
 - Treatment-related leukemia
 - First relapse
 - CR2 and beyond, if not previously evaluated

Acute Lymphoblastic Leukemia (ALL)

(adult defined as ≥ 40 years)

- High-resolution HLA typing is recommended at diagnosis for all patients
- HCT consultation should take place early after initial diagnosis for all patients with ALL, including:
 - Primary induction failure
 - Measurable (also known as minimal) residual disease after initial therapy
 - CR1
 - First relapse
 - CR2 and beyond, if not previously evaluated

Myelodysplastic Syndromes (MDS)

- High-resolution HLA typing is recommended at diagnosis for all patients
- Any intermediate or high IPSS or IPSS-R 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 Myeloid 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)
- T3151 mutation

Myeloproliferative Neoplasms (MPN)

(including *BCR-ABL*-negative myeloproliferative neoplasm and later stages of polycythemia vera and essential thrombocytosis)

- High-resolution HLA typing is recommended at diagnosis for all patients
- Intermediate- or high-risk disease, including:
 - High-risk cytogenetics
 - Poor initial response or at progression

Myelofibrosis (MF)

- DIPSS Intermediate-2 (INT-2) and high risk disease
- DIPSS Intermediate-1 (INT-1) with low platelet counts, refractory, red blood cell transfusion dependent, circulating blast cells > 2%, 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

Chronic Lymphocytic Leukemia (CLL)

- Resistance or intolerance to BTK inhibitors and/or BCL2 inhibitors

Pediatric Acute Leukemias and Myelodysplasia

Acute Myeloid Leukemia (AML)

- High-resolution HLA typing is recommended at diagnosis for all patients
- Early after initial diagnosis, all patients with AML including:
 - Age < 2 years at diagnosis
 - Primary induction failure
 - Measurable (also known as minimal) residual disease after initial therapy
 - CR1 – except favorable risk AML [defined as: *t(8;21)(q22;q22.1)*; *RUNX1-RUNX1T1*, *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q220)*; *CBFB-MYH11*, mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD*^{low}, biallelic mutated *CEBPA*]
 - Monosomy 5 or 7
 - Treatment-related leukemia
 - First relapse
 - CR2 and beyond, if not previously evaluated

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

- Infant at diagnosis
 - Unfavorable genetics
 - Age < 3 months with any WBC, or < 6 months with WBC > 300,000 at presentation
- Primary induction failure
- Presence of measurable (also known as minimal) residual disease after initial therapy
- High/very high-risk CR1, including:
 - Philadelphia chromosome positive slow-TKI responders or with *IKZF1* deletions; Philadelphia-like
 - *iAMP21*
 - 11q23 rearrangement
- First relapse
- CR2 and beyond, if not previously evaluated
- Chimeric Antigen Receptor Therapy (CAR-T)

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

- High-resolution HLA typing is recommended at diagnosis for all patients
- Presence of measurable (also known as 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

Plasma Cell Disorders

Multiple Myeloma

- At diagnosis
- At progression and/or relapse

Light Chain Amyloidosis

- At diagnosis
- At progression and/or relapse

POEMS Syndrome (Osteosclerotic Myeloma)

- 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

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

High Grade B-cell

- MYC and BCL-2 and/or BCL-6 rearrangements
- Primary induction failure
- CR1
- First relapse
- CR2 or subsequent remission

Mantle Cell

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

Mature T-cell

- CR1
- First relapse

Other High-risk Lymphomas

- At diagnosis

Other Malignant Diseases

Germ Cell Tumors

- Poor initial response
- Short initial relapse

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 CR 2

Medulloblastoma

- First relapse or CR2

Non-Malignant Disorders

Immune Deficiency Diseases

(including severe combined immunodeficiency syndromes, Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, severe congenital 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

Hemoglobinopathies

Sickle Cell Disease

- Children with available matched sibling donor
- All patients with aggressive course (stroke, end-organ complications, frequent pain crises)
- All patients with an alternative donor option and any of the following:
 - Stroke or silent cerebral infarct or cognitive impairment > 24 hours
 - ≥ 2 episodes of acute chest syndrome/2-year period [or] recurrent acute chest syndrome
 - Regular red blood cell transfusion therapy (8 or more per year)
 - Tricuspid valve regurgitant jet (TRJ) velocity ≥ 2.7 m/sec
 - Chronic pain ≥ 6 months (leg ulcers, avascular necrosis)
 - Abnormal transcranial Doppler (TCD) velocity of ≥ 200 cm/sec or > 185 cm/sec with intracranial vasculopathy
 - Silent cerebral infarct
 - ≥ 3 severe vaso-occlusive pain crises per 2-year period

Transfusion-dependent Thalassemias

- At diagnosis

Hemophagocytic Lymphohistiocytosis (HLH)

- At diagnosis

Severe Aplastic Anemia and Other Marrow Failure Syndromes

(including Fanconi anemia, Diamond-Blackfan anemia, Shwachman-Diamond syndrome and others)

- At diagnosis

Systemic Sclerosis

- At diagnosis or with diffuse disease, with increasing skin tightness score (modified Rodnan skin score, [mRSS]) and evidence of decrease (< 80%) in % predicted pulmonary function tests: forced vital capacity (FVC) and/or diffusion capacity (DLCO)

Multiple Sclerosis (MS)

After MS relapse, with ≥ 2 relapse episodes in past 3 years, while on disease modifying therapy. Refer patient prior to progression of severe disability: patient must be able to walk 100 meters (with unilateral assistance: cane, crutch or brace)

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Appendix A

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.

Kurtzke JF. *Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS)*. Neurology 1983;33(11):1444-1452.

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>

Appendix B

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.

Appendix C

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).

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.

Salit, RB & Deeg HJ. Transplant decisions in patients with myelofibrosis: should mutations be the judge? *Biol Blood Marrow Transplant*. 2018; 24: 649-58.

Appendix D

Complete Remission and Partial Remission Highlights from Revised Response Criteria for Malignant Lymphoma

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>.

Appendix E

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
 - Griselli 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)

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.

Burroughs L, Woolfrey A, Shimamura A. Shwachman-Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am*. 2009 Apr;23(2):233-48. PMID: 19327581.

Coppa GV, Gabrielli O, Zampini L, et al. Bone marrow transplantation in Hunter syndrome (mucopolysaccharidosis type II): two-year follow-up of the first Italian patient and review of the literature. *Pediatr Med Chir*. 1995 May-Jun;17(3):227-35. PMID:7567644.

Ehlert K, Roth J, Frosch M, et al. Farber's disease without central nervous system involvement: bone-marrow transplantation provides a promising new approach. *Ann Rheum Dis*. 2006;65(12):1665-6.

Filipovich A. Hematopoietic cell transplantation for correction of primary immunodeficiencies. *Bone Marrow Transplant*. 2008 Aug;42 Suppl 1:S49-S52. PMID: 18724301.

Guffon N, Bertrand Y, Forest I, et al. Bone marrow transplantation in children with Hunter syndrome: outcome after 7 to 17 years. *J Pediatr*. 2009 May;154(5):733-7.

Heese BA. Current strategies in the management of lysosomal storage diseases. *Semin Pediatr Neurol*. 2008 Sep;15(3):119-26. PMID: 18708002.

Myers KC, Davies SM. Hematopoietic stem cell transplantation for bone marrow failure syndromes in children. *Biol Blood Marrow Transplant*. 2009 Mar;15(3):279-92. PMID:19203719.

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 Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2006 Apr;117(4 Suppl):S525-53. PMID: 16580469.

Tolar J, Blazar BR, Wagner JE. Concise review: Transplantation of human hematopoietic cells for extracellular matrix protein deficiency in epidermolysis bullosa. *Stem Cells*. 2011 Jun;29(6):900-6. doi: 10.1002/stem.647. Review. PubMed PMID: 21557391.

Vellodi A, Young E, Cooper A, et al. Long-term follow-up following bone marrow transplantation for Hunter disease. *J Inherit Metab Dis*. 1999 Jun;22(5):638-48.

Vormoor J, Ehlert K, Groll AH, et al. Successful hematopoietic stem cell transplantation in Farber disease. *J Pediatr*. 2004 Jan;144(1):132-4.

Appendix F

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 IIIA/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.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

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.

Review and approval history

| Version | Date of annual review |
|---------|--|
| 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 |
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| 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 (Yescarta™ , Kite Pharma). |
| 7.0 | 11/13/2017: Corrected CAR-T prior authorization statement on page 7. |
| 8.0 | 08/02/2018: Approved by Medical Technology Assessment Committee |
| 8.0 | 09/11/2018: Approved by National Medical Care Management Committee |
| 9.0 | 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. |

| | |
|------|---|
| 9.0 | 06/06/2019: Approved by Medical Technology Assessment Committee |
| 9.0 | 06/11/2019: Approved by National Medical Care Management Committee |
| 9.0 | 12/2/2019: Corrected follicular lymphoma indication on page 10. Updated supporting references. |
| 10.0 | 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. |
| 10.0 | 8/6/2020: Approved by Medical Technology Assessment Committee |
| 10.0 | 8/11/2020: Presented to National Medical Care Management Committee |
| 10.0 | 11/11/2020: Updated minimal/measurable disease terminology |
| 11.0 | 6/15/2021: Annual Review with Optum Stem Cell Transplantation Expert Panel. No revisions. |
| 11.0 | 9/9/2021: Approved by Medical Technology Assessment Committee |
| 11.0 | 9/14/2021: Presented to National Medical Care Management Committee |
| 12.0 | 7/29/2022: Annual Review with Optum Stem Cell Transplantation Expert Panel. Added link to American Society of Hematology Stem Cell Transplantation in Sickle Cell Disease Guideline. Updated references. |
| 12.0 | 9/1/2022: Approved by Medical Technology Assessment Committee |
| 12.0 | 9/8/2022: Presented to National Medical Care Management Committee |
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| 12.0 | 1/10/2023: Presented to National Medical Care Management Committee |
| 13.0 | 7/12/2023: Annual Review with Optum Stem Cell Transplantation, Chimeric Antigen Receptor T-cell Therapy, and Gene Therapy Expert Panel. Added literature review and medical necessity criteria for Omidubicel only; updated NMDP/ASBMT Recommended Timing for Stem Cell Transplantation Consultation. |
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