Hematopoietic Stem Cell Transplantation

Clinical Guidelines
UN-CSTRANSPT002.E
Ohio Only

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Guideline 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. Allogenic 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.
- Repeat stem cell transplant is appropriate for primary and secondary failure to engraft and disease relapse.

- Primary failure is the failure to reach three consecutive days with a neutrophil count (absolute neutrophil count/ANC) > 500 µl (0.5 X 10^9/liter) after SCT, while secondary failure is associated with a successful SCT graft where neutrophils increase to > 500 µl (0.5 X 10^9/liter) for at least three consecutive days and subsequently decrease to a lower level until additional treatment is given to obtain engraftment. (There can be a loss of an allogeneic graft with normal blood cell counts due to autologous reconstitution. This can be confirmed with chimerism studies).
- Stem cell boost is a hematopoietic stem cell infusion (HSCI) provided to a transplant recipient to assist with hematopoietic recovery or declining donor chimerism. It is not preceded by a preparative regimen and is not considered a new transplant event. Stem cell boost is a non-standardized term and has been used interchangeably with terms such as reinfusion, support, and rescue. For the purposes of this guideline, we endorse use of the term “boost” based on the recommendation of the task force set up by the American Society for Blood and Marrow Transplantation in collaboration with National Marrow Donor Program (LeMaistre 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).
- 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
  - 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.
- 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).
- 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.
- 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). Perrot et al. (2025) published the outcomes of MIDAS, a phase 3 randomized trial evaluating an MRD-adapted consolidation strategy after quadruplet induction therapy in transplant-eligible patients with newly diagnosed myeloma. Patients who were MRD-negative at

10^{-5} sensitivity were assigned to undergo ASCT and receive Isa-KRd for two cycles or to receive Isa-KRd for six cycles. Patients who were MRD-positive at 10^{-5} sensitivity were assigned to undergo tandem ASCT or undergo ASCT and receive Isa-KRd for two cycles. The primary endpoint was an MRD-negative status at 10^{-6} sensitivity before maintenance therapy. Tandem ASCT did not lead to a significant improvement in the percentage of patients who were MRD-positive at 10^{-6} sensitivity before maintenance therapy. The results suggest that routine use of tandem ASCT may no longer be warranted after the receipt of effective induction regimens that include anti-CD38 antibodies and proteasome inhibitors. In a 2025 update on MRD in AML, Cloos et al., on behalf of the European LeukemiaNet (ELN) MRD Working Party, published an expert consensus document focused on the clinical implementation of MRD methodologies, technical considerations, integration into clinical trials, and future directions. Importantly, MRD recommendations are now tailored to specific prognostic and genetic subgroups. The panel introduced a novel qualitative MRD response category designated as optimal, warning, or high risk of treatment failure to facilitate contextual interpretation of MRD burden and its clinical relevance. Ultrahigh-sensitivity next-generation sequencing–based MRD assessment is now recommended for patients with *FLT3* internal tandem duplication–mutated AML following intensive chemotherapy and prior to allogeneic hematopoietic cell transplantation. Overall, 56 recommendations were formulated, 53 of which achieved a high level of consensus (≥90%). Collectively, these updated guidelines represent a significant advance toward harmonizing MRD assessment in AML and enhancing its clinical utility across diverse therapeutic settings. 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)

Leukemias

Leukemia more often is a cancer affecting white blood cells. Leukemia occurs most often in adults older than 55, however it is also the most common cancer in children younger than 15 years (National Cancer Institute, 2024). There are four main types of leukemia: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). The rate at which the disease progresses and how leukemic cells replace the normal blood and marrow cells differs with each type of leukemia. There also exists several uncommon or rare forms of leukemia including, but not limited to, hairy cell leukemia, B-cell prolymphocytic leukemia, and T-cell prolymphocytic leukemia (Leukemia and Lymphoma Society, 2024). There is a lack of data supporting autologous stem cell transplantation 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.

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary for the following types of leukemia:

- ALL (McNeer et al., 2019; Cavallaro et al., 2025; Holly et al., 2025; van den Berg et al., 2025; Yang et al., 2025)
  - First complete remission
  - Second or subsequent complete remission
  - Any relapse

    - Consolidation post-CART therapy
- AML (Dohner et al, 2022) (See Appendix A for risk classification by genetics at initial diagnosis)
    - Adverse-risk disease
    - Intermediate-risk disease including cytogenetic and/or molecular abnormalities not classified as favorable or adverse
    - Favorable-risk disease with inadequate clearance of MRD
- CLL
- CML
- Prolymphocytic leukemia

Allogeneic hematopoietic stem cell transplantation is considered unproven and not medically necessary for all other leukemia types.

Autologous hematopoietic stem cell transplantation may be considered medically necessary for the following types of leukemia:

- Prolymphocytic leukemia
- ALL (McNeer et al., 2019)
    - May be indicated in certain adults when there is no suitable allogeneic donor. Refer to Medical Director.
    - In pediatric patients certain cytogenetic features including hypodiploid (<44 chromosomes and iAMP21) are associated with high-risk disease and may influence the decision to transplant in first complete response (CR1). Refer to Medical Director.
- AML (Dohner et al., 2017
    - May be indicated in certain adults when there is no suitable allogeneic donor. Refer to the Medical Director.

Autologous hematopoietic stem cell transplantation is considered unproven and not medically necessary for all other leukemia types.

Myelodysplastic Syndromes & Mixed Myelodysplastic/Myeloproliferative Neoplasms

Myelodysplastic syndromes (MDS) are a collection of myeloid malignancies distinguished by one or more blood cytopenias. In the United States, MDS is diagnosed in a little over 10,000 cases annually, translating to roughly 4.4 cases per 100,000 individuals (National Cancer Institute, 2024). The World Health Organization (WHO) classifies CMML as a myelodysplastic/myeloproliferative neoplasm.

The sole curative therapy for myelodysplastic syndrome (MDS) is allogeneic hematopoietic cell transplantation (HCT). Recent prospective trials have confirmed that allogeneic HSCT confers survival benefits in patients with advanced or high-risk MDS compared with nontransplantation approaches, and the use of HSCT is increasing in older patients with good performance status. However, patients with high-risk cytogenetic or molecular mutations remain at high risk for relapse. It is unknown whether administration of novel therapies before or after transplantation may decrease the risk of disease relapse in selected populations. Ongoing and future studies will investigate revised approaches to disease risk stratification, patient selection, and post-transplantation approaches to optimize allogeneic HCT outcomes for patients with MDS (DeFilipp et al., 2023).

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary for the following:

- Myelodysplastic syndromes (MDS)
- Juvenile myelomonocytic leukemia/juvenile chronic myelogenous leukemia (JMML/JCML)
- Chronic myelomonocytic leukemia (CMML) (Swerdlow et al., 2017)

Autologous hematopoietic stem cell transplantation is considered unproven and not medically necessary for the following:

- Myelodysplastic syndromes (MDS)
- Juvenile myelomonocytic leukemia (JMML/JCML)
- Chronic myelomonocytic leukemia (CMML) (Swerdlow et al., 2017)

Note: On March 6, 2024, CMS issued a final decision under National Coverage Determination (NCD) 110.23 to expand Medicare coverage for allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with MDS dependent on prognostic risk scores. See Appendix B for prognostic risk scores for myelodysplastic syndrome.

Myeloproliferative Disorders

Myelofibrosis is a rare disorder that impairs normal blood cell formation, resulting in splenomegaly, anemia, and fibrosis. Myelofibrosis develops when a mutation occurs in a hematopoietic stem cell, the genetic material in the cell starts to proliferate and disrupts normal blood synthesis, leading to the development of myelofibrosis. The identification of adverse karyotypes is evolving. New clinical molecular scoring systems may become useful in determining post-transplant prognosis. Myelofibrosis occurs in approximately 0.25 cases per 100,000 (Manning, 2022).

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Primary myelofibrosis and related conditions (e.g., polycythemia vera) in patients with Intermediate-2 or High-Risk score using the Dynamic International Prognostic Scoring System Plus (DIPSS) (Gagelman et al., 2019). See Appendix C
- Secondary myelofibrosis
  - Allogeneic transplant evaluation approved for patients with polycythemia vera or essential thrombocythemia.

Autologous hematopoietic stem cell transplantation is considered unproven and not medically necessary for the following:

- Primary myelofibrosis and related conditions (Gagelman et a., 2019)
- Secondary myelofibrosis

Brain Tumors

Brain tumors comprise 85% to 90% of primary central nervous system (CNS) tumors. The combined incidence of brain and other CNS tumors in the United States is 6.2 per 100,000 people per year, with a mortality rate of 4.4 deaths per 100,000 people per year (National Cancer Institute, 2024). The main types of brain tumors include anaplastic astrocytoma, brain stem glioma, ependymoma, germinoma, glioblastoma multiforme, medulloblastoma, oligodendroglioma, pineoblastoma, embryonal tumors with multi-layered rosettes (formerly known as primitive neuroectodermal tumor).

Allogeneic hematopoietic stem cell transplantation is considered unproven and not medically necessary for brain tumors including but not limited to the following:

- Anaplastic astrocytoma
- Brain stem glioma
- Ependymoma
- Germinoma
- Glioblastoma multiforme (GBM)
- Medulloblastoma
- Oligodendroglioma
- Pineoblastoma
- Embryonal tumors with multi-layered rosettes (ETMR)

Autologous hematopoietic stem cell transplantation may be considered medically necessary for the following brain tumors:

- Medulloblastoma
- Oligodendroglioma
- Pineoblastoma
- Embryonal tumors with multi-layered rosettes (ETMR)
- Glioblastoma multiforme (GBM)
  - May be considered in infants. Refer to Medical Director.

Autologous hematopoietic stem cell transplantation is considered unproven and not medically necessary for all other brain tumors including but not limited to the following:

- Anaplastic astrocytoma
- Brain stem glioma
- Ependymoma
- Germinoma

Germ Cell Tumors

Germ cell tumors arise from primordial germ cells. Testicular and sacrococcygeal GCTs arising during early childhood characteristically have deletions at chromosome arms 1p and 6q and gains at 1q, and they lack the isochromosome 12p that is highly characteristic of malignant GCTs of adults. Testicular GCTs also may demonstrate loss of imprinting. Ovarian GCTs from older females characteristically have deletions at 1p and gains at 1q and 21. Dysregulation of microRNAs have been linked to GCTs. Because GCTs may contain benign and mixed malignant elements in different areas of the tumor, extensive sectioning is essential to confirm the correct diagnosis. The many histologically distinct subtypes of GCTs include teratoma (mature and immature), endodermal sinus tumor, and embryonal carcinoma. Teratomas occur in many locations, presenting as masses. They are not associated with elevated markers unless malignancy is present. The sacrococcygeal region is the most common site for teratomas. Sacrococcygeal teratomas occur most commonly in infants and may be diagnosed in utero or at birth, with most found in girls. The rate of malignancy in this location varies, ranging from <10% in children younger than 2 months to >50% in children older than 4 months. Germinomas occur intracranially, in the mediastinum, and in the gonads. In the ovary, they are called dysgerminomas, and in the testis, they are called seminomas. They usually are tumor-marker–negative masses despite being malignant. Endodermal sinus or yolk sac tumor and choriocarcinoma appear highly malignant by histologic criteria. Both occur at gonadal and extragonadal sites. Embryonal carcinoma most often occurs in the testes. Choriocarcinoma and embryonal carcinoma rarely occur in the pure form and are usually found as part of a mixed malignant GCT. Complete surgical excision of the tumor usually is indicated, except for patients with intracranial tumors, for whom the primary therapy consists of radiation therapy and chemotherapy. High-dose chemotherapy followed by autologous stem cell rescue may also be considered (Herzog & Huh, 2025).

Allogeneic hematopoietic stem cell transplantation is considered unproven and not medically necessary for germ cell tumors including but not limited to the following:

- Testicular germ cell tumor
- Extragonadal germ cell tumor
- Seminoma
- Choriocarcinoma
- Embryonal carcinoma
- Mixed germ cell tumors
- Teratoma
- Yolk-sac tumor (endodermal sinus tumor)
- Germ cell tumor of the ovary

Autologous and tandem autologous hematopoietic stem cell transplantation may be considered medically necessary for the following:

- Testicular germ cell tumor
- Extragonadal germ cell tumor
- Seminoma
- Choriocarcinoma
- Embryonal carcinoma
- Mixed germ cell tumors
- Teratoma
- Yolk-sac tumor (endodermal sinus tumor)
- Germ cell tumor of the ovary

Multiple Myeloma

Multiple myeloma (MM) is a plasma cell malignancy in which monoclonal plasma cells proliferate in bone marrow, resulting in an overabundance of monoclonal paraprotein (M protein), destruction of bone, and displacement of other hematopoietic cell lines. MM is part of a spectrum of diseases including monoclonal gammopathy of undetermined significance (MGUS) and plasma cell leukemia. Nearly all patients with multiple myeloma evolve from MGUS. Since MGUS is asymptomatic, over 50% of individuals who are diagnosed with MGUS have had the condition for over 10 years prior to the clinical diagnosis. MGUS progresses to multiple myeloma or related malignancy at a rate of 1% per year. In some patients, an intermediate asymptomatic but more advanced pre-malignant stage referred to as smoldering multiple myeloma (SMM) can be recognized clinically. SMM progresses to multiple myeloma at a rate of approximately 10% per year over the first 5 years following diagnosis, 3% per year over the next 5 years, and 1.5% per year thereafter. This rate of progression is influenced by the underlying cytogenetic type of disease; patients with t(4;14) translocation, del(17p), and gain(1q) are at a higher risk of progression from MGUS or SMM to multiple myeloma (Rajkumar, 2022). See Appendix D for criteria for diagnosis of 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. These 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 the Medical Director.

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary for multiple myeloma in 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 cytogenics [presence of at least one of the following: del(17p), t(4;14) or t(14;16) determined by FISH]
  - 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)

Autologous hematopoietic stem cell transplantation may be considered medically necessary in multiple myeloma in the following circumstances:

- Single autologous
- Tandem (autologous followed by autologous)

- Tandem (autologous followed by allogeneic) in early relapse [less than 24 months] after primary therapy that included an autologous SCT or with high-risk features (i.e., cytogenics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) if they respond favorably to salvage therapy (Giralt, 2015).

Plasma Cell Disorders

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Waldenstrom macroglobulinemia
- May be appropriate in a clinical trial for AL- Amyloidosis

Allogeneic hematopoietic stem cell transplantation is unproven and not medically necessary in all other circumstances including but not limited to:

- Monoclonal gammopathy of uncertain significance (MGUS)
- Polyneuropathy organomegaly endocrinopathy monoclonal gammopathy skin defects syndrome (POEMS)
- Solitary plasmacytoma

Autologous hematopoietic stem cell transplantation may be considered medically necessary for the following:

- AL-Amyloidosis
- POEMS (D'Souza et al., 2012; Ji et al., 2012; Li et al., 2013)
- Waldenstrom macroglobulinemia

Autologous hematopoietic stem cell transplantation is unproven and not medically necessary in all other circumstances including but not limited to:

- MGUS
- Solitary plasmacytoma

Monoclonal Gammopathy of Renal Significance (MGRS)

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 a 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 (Fermand et al., 2013).

Autologous hematopoietic stem cell transplantation may be considered medically necessary for MGRS in patients who meet the following criteria:

- Have failed chemotherapy targeting the underlying B-cell clone

  AND
- Have sufficient renal function to tolerate high-dose chemotherapy

Allogeneic hematopoietic stem cell transplantation is unproven and not medically necessary in MGRS.

Hodgkin Lymphoma

Hodgkin lymphoma (HL) is an uncommon malignancy of B-cell origin. Most patients are diagnosed between ages 15 and 30 years, followed by another peak in adults ≥ 55 years. In 2024, an estimated 8570 people will be diagnosed with HL in the United States and 910 people will die from the disease (American Cancer Society, 2024). The World Health Organization (WHO) classification divides HL into two main types: classic Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). In Western countries, CHL accounts for 95% and NLPHL accounts for 5% of all HL. While the WHO has maintained the term NLPHL, the International Consensus Classification (ICC) has now replaced the term NLPHL with the term nodular lymphocyte predominant B-cell lymphoma (NLPBL) based on biological and clinical differences with CHL. The past few decades have seen significant progress in the management of HL. The advent of more effective treatment options has improved the 5-year survival rates, which have been unmatched in any other cancer over the past 4 decades. It is among the most curable of malignancies with modern treatments, and newly diagnosed HL has a very high likelihood of being cured with appropriate management. In fact, cure rates for HL have increased so markedly that overriding treatment considerations often relate to long-term toxicity. Clinical trials still emphasize improvement in cure rates for patients with advanced disease, but the potential long-term effects of treatment remain an important consideration (Campo et al., 2022).

Autologous hematopoietic stem cell transplantation is considered medically necessary for Hodgkin lymphoma.

Allogeneic hematopoietic stem cell transplantation is considered medically necessary for Hodgkin lymphoma.

Non-Hodgkin Lymphoma (NHL)

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies of the lymphoreticular system subdivided into indolent, aggressive, and highly aggressive disease. The therapeutic regimen varies with specific lymphoma subtype and pathologic stage. There are approximately 60 different NHL subtypes. NHL is the seventh most common neoplasm in the U.S. with >80,000 new cases annually. Incidence increases with age with the majority of patients older than 60 years. In the U.S. and Europe, diffuse large B-cell lymphoma (DLBCL) is the most common subtype (30% of the cases) followed by follicular lymphoma (FL) comprising 25% of cases. In patients with HIV, NHL is the most common tumor followed by Kaposi sarcoma. The presence of B symptoms such as unexplained weight loss, fever, fatigue, and night sweats are seen typically in aggressive lymphomas. Aggressive lymphomas have acute or subacute presentation with increasing size of the mass and B symptoms. Indolent lymphomas have a more chronic course, with asymptomatic lymphadenopathy and/or slowly progressive cytopenias. Initial laboratory evaluation may be entirely normal. Elevated serum LDH may be seen in aggressive lymphoma or in indolent lymphoma with high disease burden. In cases of highly aggressive NHL (e.g., Burkitt lymphoma), spontaneous tumor lysis syndrome (TLS) may be seen, characterized by hyperkalemia, hyperuricemia, hypocalcemia, hyperphosphatemia, and acidosis. TLS can be life threatening and is considered a medical emergency (Alaggio et al., 2022).

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Small B-cell lymphocytic lymphoma
- 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

Autologous hematopoietic stem cell transplantation may be considered medically necessary for the following:

- 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

For autologous hematopoietic stem cell transplants, tumors must be chemosensitive which is defined as a complete or partial response based on the Cheson criteria. See Appendix E

Note: Autologous hematopoietic stem cell transplantation is not considered standard of care for small lymphocytic lymphoma and should be treated in the same manner as chronic lymphocytic leukemia (CLL). Refer requests to Medical Director.

Other Malignancies

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Blastic plasmacytoid dendritic cell neoplasm (Dietrich et al., 2014)
- Rhabdomyosarcoma/soft tissue sarcoma may be appropriate as part of a clinical trial (Stiff et al., 2010). Refer to Medical Director.

Allogeneic hematopoietic stem cell transplantation is unproven and not medically necessary in all other circumstances including but not limited to the following:

- Atypical teratoid rhabdoid tumors (Nikolaides et al., 2010)
- Epithelial ovarian cancer
- Ewing tumor (Ewing sarcoma)
- Neuroblastoma
- Osteogenic sarcoma
- Renal cell carcinoma
- Retinoblastoma
- Supratentorial ependymoma (Venkatramani et al., 2013)
- Wilms tumor (Brown et al., 2010; Campbell et al., 2004).

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- Ewing tumor (Ewing sarcoma)
- Neuroblastoma
- Retinoblastoma
- Supratentorial ependymoma (Venkatramani et al., 2013)
- Atypical teratoid rhabdoid tumors (Nikolaides et al., 2010)
  - Tandem auto may be indicated as part of a clinical trial
- Rhabdomyosarcoma/soft tissue sarcoma (Stiff et al., 2010)
  - May be appropriate as part of a clinical trial. Refer to Medical Director
- Wilms tumor (Brown et al., 2010; Campbell et al., 2004)
  - May be appropriate in relapsed disease as part of a clinical trial. Refer to Medical Director

Autologous hematopoietic stem cell transplantation is considered unproven and not medically necessary for all other malignancies including but not limited to:

- Blastic plasmacytoid dendritic cell neoplasm (Dietrich et al., 2014)
- Epithelial ovarian cancer
- Osteogenic sarcoma

- Renal cell carcinoma

Hematological Disorders

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Aplastic anemia
- Diamond-Blackfan syndrome
- Chronic granulomatous disease
- Congenital agranulocytosis (Kostmann syndrome)
- Congenital amegakaryocytic thrombocytopenia
- Dyskeratosis congenita
- Fanconi anemia
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Shwachman-Diamond syndrome
- Sickle cell disease (SCD) (Kanter et al., 2021)
- Thalassemia major

Autologous hematopoietic stem cell transplantation is unproven and not medically necessary in hematologic disorder including but not limited to the following:

- Aplastic anemia
- Diamond-Blackfan syndrome
- Chronic granulomatous disease
- Congenital agranulocytosis (Kostmann syndrome)
- Congenital amegakaryocytic thrombocytopenia
- Dyskeratosis congenita
- Fanconi anemia
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Shwachman-Diamond syndrome
- Sickle cell disease (SCD)
- Thalassemia major.

Immunodeficiency Syndromes

Primary immunodeficiency diseases (PIDDs) are a collection of >200 rare disorders involving the absence or malfunction of integral parts of the immune system. The etiologies of PIDDs are not communicable in the infectious sense but vertically transmissible via transfer of inherited genetic defects. Although some defects affect a single part of the immune system, others cause multicomponent breakdown of combined innate and cellular immune responses and suggest the interplay of epigenetic influences. To be considered a PIDD, the cause must not be secondary to another disease, drug/chemical, or environmental exposure. Primary immunodeficiency disease onset may occur at birth, as most do, or at any subsequent developmental stage and may affect anyone, with only specific regard to gender or ethnicity (Ferri, 2024).

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- CD40 ligand deficiency
- Chediak-Higashi syndrome
- Hemophagocytic lymphohistiocytosis (HLH) (same as familial erythrophagocytic lymphohistiocytosis - FEL)
- Leukocyte adhesion deficiency
- Omenn syndrome
- Wiskott-Aldrich syndrome
- X-linked lymphoproliferative syndrome
- Lysosomal storage diseases
- 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.
- Gaucher disease type I
    - 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 (Tirelli et al., 2024)
    - 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 (Naumchik et al., 2020)
    - 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.

Autologous hematopoietic stem cell transplantation is unproven and not medically necessary for immunodeficiency syndromes including but not limited to the following:

- 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)
- Wiskott-Aldrich syndrome
- X-linked lymphoproliferative syndrome
- Gaucher disease type I
- Niemann-Pick type B (Tirelli, 2024)
- Fucosidosis (Naumchik et al., 2020)
- Lysosomal storage diseases

Autoimmune Diseases

Hematopoietic stem cell transplantation (HSCT) has been increasingly used to treat patients affected by severe and refractory autoimmune diseases (ADs). The majority of such patients have chronic diseases, which impact quality-of-life and can shorten life expectancy but are rarely life-threatening in the short-term. Multiple sclerosis (MS) and systemic sclerosis (SSc) account for approximately 80% of transplants performed for ADs, where HSCT has become an integral and standard-of-care component of treatment algorithms (Alexander et al., 2022).

HSCT exerts its therapeutic effect in autoimmune diseases through various mechanisms, including the immunosuppressive conditioning regimen able to eradicate the autoreactive immunologic memory, and the regeneration and renewal of the immune system, leading to the re-induction of immune tolerance to rewire aberrant immune response toward self-antigens (Lima-Junior et al. 2021; Cencioni et al. 2022). The development of an immunological balance allows long-term disease remission (Muraro et al 2017).

Allogeneic hematopoietic stem cell transplantation is unproven and not medically necessary in the following autoimmune disease (not an exhaustive list):

- Multiple sclerosis
- Systemic sclerosis (scleroderma)

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Crohn's disease
  - Not a 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.
- Rheumatoid arthritis
  - Not a 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)
  - Not a 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

Autologous hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Crohn's disease
  - Not a 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 (Alexander et al., 2022; Cencioni et al., 2022; Cohen et al., 2019; Muraro et al., 2017)
  - Patient must meet the definition of relapsing-remitting (RR) or secondary progressive (SP) multiple sclerosis. See Appendix F
  - Expanded Disability Status Scale (EDSS) score between 2.0 and 6.0. See Appendix G
  - Patient is unable to take or has failed treatment with one or more disease-modifying therapies
  - Evidence of either of the following while being treated with DMT:
    - 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
- Rheumatoid arthritis
  - Not a 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)
  - Not a 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) (Alexander and Greco, 2022; Henes et al., 2021; Sakkas et al., 2025; Santos, 2025)
  - Adult patients at least 18 years of age
  - Diffuse cutaneous systemic sclerosis (dcSSc)
  - Disease duration ≤ 5 years from first non-Raynaud's symptom
  - Modified Rodnan skin thickness score (mRSS) ≥ 15-20 (See Appendix H)
  - Evidence of progressive internal organ involvement such as
    - Decline in FVC > 10%
    - DLco < 80%
    - Progressive interstitial lung disease (ILD) on high-resolution computed tomography (HRCT)

  AND
  - Patient does not have ANY of the following:
    - FVC < 45% of predicted value
    - Creatinine clearance < 40 ml/min
    - Pulmonary arterial hypertension
    - Constrictive pericarditis

    - Cardiac tamponade
    - Left ventricular ejection fraction < 50%
- Patient is felt to be an appropriate candidate for autologous transplant by the treating facility

Inherited Metabolic Disorders

Allogeneic hematopoietic stem cell transplantation may be considered medically necessary in the following:

- Adrenoleukodystrophy
- Epidermolysis bullosa
- Globoid cell leukodystrophy (Krabbe disease)
- Hurler syndrome (MPS I)
- Hunter syndrome (MPS II)
- Mannosidosis
- Maroteaux-Lamy syndrome (MPS VI)
- Metachromatic leukodystrophy
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE) (Filosto et al., 2012; Halter et al., 2011)
- Osteopetrosis
- Rett syndrome

Autologous hematopoietic stem cell transplantation is unproven and not medically necessary for inherited metabolic disorders including but not limited to the following:

- Adrenoleukodystrophy
- Epidermolysis bullosa
- Globoid cell leukodystrophy (Krabbe disease)
- Hurler syndrome (MPS I)
- Hunter syndrome (MPS II)
- Mannosidosis
- Maroteaux-Lamy syndrome (MPS VI)
- Metachromatic leukodystrophy
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE) (Filosto et al., 2012; Halter et al., 2011)
- Osteopetrosis
- Rett syndrome

Cardiac Conditions

Allogeneic and autologous hematopoietic stem cell transplantation are unproven and not medically necessary for cardiac conditions. Stem cell transplantation would only be considered for approval under a clinical trial if the members benefit plan supports participation in a clinical trial.

Additional Conditions

Allogeneic stem cell transplantation may be considered medically necessary in rare and unusual conditions. See Appendix I

Note: If there is a condition found within Appendix G 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 and 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. **Note**: Refer to Medical Director if questions remain.

- 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 regiment and there must be documented evidence of viral load suppression.
- Serum creatinine > 2.5 mg/dL (≥ 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 SCT 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. **Note:** 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).

Donor Lymphocyte Infusion

Donor lymphocyte infusion (DLI), also known as donor leukocyte or buffy-coat infusion, is an adoptive immunotherapy administered after allogeneic hematopoietic stem cell transplantation (HSCT) to induce a graft-versus-leukemia or graft-versus-tumor effect. In this approach, lymphocytes collected from the original stem cell donor are infused to help eliminate residual or recurrent malignant cells without the need for additional high-dose chemotherapy. DLI is used to treat relapsed, persistent, or refractory hematologic malignancies in patients who previously received a transplant from the same donor (Pagliuca et al., 2024).

Yang et al. (2024) conducted a multicenter retrospective study comparing prophylactic versus preemptive modified donor lymphocyte infusion (DLI) in patients with acute leukemia who had high-risk features for relapse. High-risk criteria included failure to achieve complete remission after two induction cycles, advanced disease at transplantation, minimal residual disease (MRD) positivity at transplant, or adverse genetics per NCCN guidelines. All patients had previously received myeloablative conditioning and allogeneic HSCT, followed by infusion of donor-derived peripheral blood or bone marrow cells without ex vivo T-cell depletion. Standard GVHD prophylaxis included cyclosporine A, methotrexate, and low-dose mycophenolate mofetil.

Prophylactic DLI was administered three months post-HSCT to patients in continuous complete remission with undetectable MRD, complete chimerism, and no prior grade >II acute GVHD. Preemptive DLI was given after stopping immunosuppression when MRD became positive during morphological remission.

Among 271 evaluable patients (95 prophylactic; 176 preemptive), the prophylactic cohort demonstrated superior progression-free survival (63.4% vs. 53.0%; p=0.026) and a trend toward improved overall survival (65.2% vs. 57.0%; p=0.14). Relapse incidence was also lower in the prophylactic group (25.3% vs. 36.7%; p=0.02). Rates of grade III–IV acute GVHD, chronic GVHD, and non-relapse mortality were similar between groups. Overall, early scheduled prophylactic DLI was associated with reduced post-transplant relapse and improved long-term outcomes compared with preemptive DLI in high-risk acute leukemia.

National Comprehensive Cancer Network (NCCN) addresses DLI in several Clinical Practice Guidelines including Acute Lymphoblastic Leukemia (V2.2025), Chronic Myeloid Leukemia (V1.2026), Multiple Myeloma (V5.2026), and Myelodysplastic Syndromes (V3.2026). Each of these guidelines consider DLI a treatment option for relapsed or refractory disease.

Donor lymphocyte infusion (DLI) is medically necessary following a medically necessary allogeneic hematopoietic stem cell transplantation (HSCT) for a hematologic malignancy when the following criteria are met:

- Donor lymphocytes are collected from the original hematopoietic stem cell donor
- Donor lymphocyte infusion is intended for one of the following indications:
  - Management of a refractory, persistent, or relapsed hematologic malignancy
  - To enhance conversion from mixed to full donor chimerism in the setting of confirmed relapsed disease
  - A planned strategy to prevent relapsed hematologic malignancy in patients at an elevated risk for relapse

Umbilical Cord Blood Stem Cell Transplantation

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 X 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 onlv (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. Omidubicel is prepared as a cell suspension for intravenous infusion. A single dose consists of a Cultured Fraction (CF): a minimum of 8.0×10^8 total viable cells of which a minimum of 8.7% is CD34+ cells and a minimum of 9.2×10^7 CD34+ cells, and a Non-cultured Fraction (NF): a minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 CD3+ cell. 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 onlv (Omisirge ®) may be considered medically necessary in patients with a hematologic malignancy when all of the following are met:

- Patient is 12 years of age or older
- Is a candidate for myeloablative allogeneic HSCT
- Has no readily available matched sibling or matched unrelated donor
- The medication is being requested to reduce the time to neutrophil recovery and incidence of infection
- Following a comprehensive evaluation of the clinical condition it is felt this is the best choice of cell source for this particular patient

In December 2025, the FDA approved Omidubicel onlv (Omisirge®) for use in adults and pediatric patients 6 years and older with severe aplastic anemia (SAA) following reduced intensity conditioning. The efficacy of Omisirge in patients SAA was evaluated in NCT 03173937 (study 17- H-0091), an open-label, single center study enrolling patients with SAA who had intolerance or failure to respond to immunosuppressive therapy and availability of at least one ≥ 4/8 human leukocyte antigen (HLA)-matched (HLA-A, B, C and DR loci) cord blood unit. Patients were excluded if there was availability of an HLA identical (12/12) matched related or unrelated donor. In total, 17 patients were treated with Omisirge; 14 patients were treated with Omisirge alone and 3 patients were treated with both Omisirge and haploidentical CD34+ cells. The 14 patients who were transplanted with Omisirge alone were included in the efficacy evaluation. All patients received reduced intensity conditioning which included cyclophosphamide, fludarabine, TBI and horse-ATG. GvHD prophylaxis was administered according to institutional guidelines. Median absolute neutrophil count at baseline was 0.3 x109 /L (range, 0.0 – 1.0) and median platelet count at baseline was 35 x 109 /L (range, 10-89). Hematopoietic stem cell transplantation (HCT) specific comorbidity index was ≥ 3 in 76% and 0-2 in 24% of patients. Twelve percent of patients received 4/8 HLA match, 59% 5/8 HLA match, 18% 6/8 HLA match, 6% 7/8 HLA match and 6% 8/8 HLA match. The primary efficacy outcome measure was the incidence of early and sustained neutrophil recovery, defined as ANC ≥500 cells/µl for 3 consecutive measurements on different days by Day 26, maintained at Days 42 and 100 post-transplant. At 100 days post-transplant, 12 patients (86%; 95% CI 57%, 98%) had maintained neutrophil recovery. Other secondary efficacy outcomes included time to neutrophil recovery (median days 11, min-max 7-20), and time to RBC transfusion independence (median days 58.5, min-max 42-446). Eleven patients (79%) achieved platelet transfusion independence at a median of 53 days (min-max 43-93) (FDA, 2025; Gamida Cell, 2025).

Omidubicel onlv (Omisirge®) is considered medically necessary in patients with a diagnosis of severe aplastic anemia when all the following are met:

- Patient is 6 years of age or older
- Has no readily available matched sibling or matched unrelated donor
- Is a candidate for reduced intensity conditioning
- Omisirge is being requested to reduce the time to neutrophil recovery and the incidence of infection
- Following a comprehensive evaluation of the clinical condition, it is felt umbilical cord blood is the best choice of cell source for this patient

Complications

Graft versus Host Disease

Graft versus host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplant (HSCT). There are two primary categories of GVHD: acute and chronic. Chronic GVHD is beyond the scope of this guideline.

Acute GVHD (aGVHD) is traditionally defined as occurring within the first 100 days following transplant. Up to 50% of patients receiving transplants from an HLA-matched related donor will develop aGVHD. The occurrence is typically higher in unmatched donors (Justiz Valliant et al., 2024). Acute GVHD affects the skin, liver and GI tract and is characterized by macropapular rash, jaundice, and diarrhea. Diagnosis is based on clinical findings of skin involvement followed by evidence of gastrointestinal (GI) tract and liver involvement. Organ-appropriate testing such as stool infectious disease tests, imaging studies, and/or viral testing are pursued to rule out non-GVHD causes of the symptoms followed by organ-directed biopsy as clinically indicated to support the presence of aGVHD or to exclude other diagnoses. Each organ is staged individually: skin is assigned a stage based on body surface involved; the GI tract is staged based on the severity of diarrhea; and the liver is staged based on bilirubin level (Hayes, 2024). See Appendix J for an example of commonly used criteria for the staging and grading of adults and children with aGVHD.

Aside from HLA mismatch, a number of factors are associated with an increased risk of moderate to severe aGVHD including unrelated donor, older age of donor or recipient, female donor for a male recipient, intensity of the transplant conditioning regimen, and receiving total body irradiation (TBI) as part of the conditioning regimen. In addition to controlling as many of these risk factors as possible, other prophylactic strategies include immunosuppression with calcineurin inhibitors (i.e., cyclosporine, tacrolimus), methotrexate, or mycophenolate mofetil, alone or in combination, and prophylaxis with antithymocyte globulin or anti-T-lymphocyte globulin. In December 2021, The FDA approved abatacept (Orencia®), a T-cell costimulatory inhibitor, for the prophylaxis of aGVHD in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing HSCT from a matched or 1 allele-mismatched unrelated donor. Abatacept is the first drug approved to prevent aGVHD. Overall incidence has decreased due to more effective prophylactic strategies including effective calcineurin inhibitor (CNI) regimens and post-transplant cyclophosphamide (PTCy).

The goals of treatment for GVHD are symptom management and prevention of further damage to the body's organs. Immunosuppression with corticosteroids forms the basis of therapy. Treatment decisions are determined by the severity of the patient's symptoms as well as concerns about complications. Patients with grade I mild skin-only aGVHD are treated with non-systemic topical corticosteroids while patients with grade II – IV disease typically require systemic treatment either alone or in conjunction with topical steroids. At the present time, the National Comprehensive Cancer Network (NCCN®) Hematopoietic Cell Transplantation Guideline (V2.2026) recommends the addition of other systemic agents in conjunction with systemic corticosteroids as first-line therapy for aGVHD should only be done in the context of a well-designed clinical trial.

Despite first-line high-dose steroids, approximately 40% of patients will not respond to treatment resulting in the diagnosis of steroid-refractory aGVHD (SR-aGVHD). Consensus has yet to develop for the management of SR-aGVHD, and prognosis at six months has been estimated at around 50% (Zeiser et al., 2023). A number of systemic agents are commonly used in conjunction with immunosuppressive agents and corticosteroids to treat steroid-refractory SR-aGVHD. Ruxolitinib (Jakafi) is FDA-approved for the treatment of SR-aGVHD in adults and children

(age ≥12 years) and is a NCCN category 1 systemic agent suggested for use in conjunction with corticosteroids. Alternative agents suggested by NCCN include:

- Alemtuzumab
- Alpha-1 antitrypsin
- Anti-thymocyte globulin (ATG)
- Basilixumab
- Calcineurin inhibitors (e.g., tacrolimus, cyclosporine)
- Etanercept
- Extracorporeal photopheresis (ECP)
- Infliximab
- mTOR inhibitors (e.g., sirolimus)
- Mycophenolate mofetil
- Pentostatin
- Tocilizumab
- Urinary-derived human chorionic gonadotropin/epidermal growth factor (uhCG/EGF)
- Vedolizumab

NCCN Guidelines for Hematopoietic Cell Transplantation (V2.2026) indicate there is insufficient evidence to recommend one of these alternative agents as preferred over another noting these are the most commonly used agents among NCCN Member Institutions. The selection of therapy for SR-aGVHD should be based on physician experience, agent's toxicity profile, the effect of prior treatment, drug interaction, convenience/accessibility, and patient tolerability.

Remestemcel-L-rknd (Ryoncil®) is the first therapy approved by the FDA for treatment of SR-aGVHD in children 2 months of age and older, including adolescents and teenagers. Ryoncil is an allogeneic bone-marrow-derived mesenchymal stromal cell (MSC) suspension administered intravenously twice per week for 4 consecutive weeks. Infusions should be administered at least 3 days apart. Patients exhibiting a complete response (CR) at day 28 ± 2 days require no further treatment, while those with partial or mixed response may receive repeat administration of Ryoncil once per week for an additional 4 weeks (4 infusions total). Recurrence of GVHD following a CR may be treated with Ryoncil twice a week for an additional 4 consecutive weeks (8 infusions total).

Kurtzberg et al. (2020) report the results of a phase 3, single-arm, open-label, prospective, multicenter study (NCT02336230) conducted at 20 centers in the United States. The study was designed to evaluate the efficacy and safety of remestemcel-L-rknd in pediatric patients with primary SR-aGVHD who were naïve to other immunosuppressant therapies for aGVHD. The primary efficacy endpoint was overall response (OR) at day 28. Day 28 OR is an early indicator of subsequent long-term response and is now generally accepted as an appropriate surrogate for clinical outcomes (Martin et al., 2009). Children 2 months to 17 years of age (n = 54) with SR-aGVHD grade B to D (excluding skin-only grade B) received remestemcel-L-rknd intravenously at a dose of 2 x 10^6 MSCs/kg body weight, twice weekly, for 4 consecutive weeks. All initial infusions were completed by day 28 ± 2 days. Those with partial (PR) or mixed response (MR) on day 28 could receive continued therapy of 4 once-weekly infusions at the same initial dose of 2 x 10^6 MSCs/kg body weight beginning within 1 week following the day 28 assessment. The median age of patients was 7 years, 63.6% were male, and 76% of patients received a HSCT from an unrelated donor. The median time from onset of aGVHD to first remestemcel-L-rknd infusion was 12 days, and median time for establishing onset of steroid failure to first remestemcel-L-rknd infusion was 3.5 days. At baseline, 47.4% of patients had grade D aGVHD; 89.1% had severe disease, defined as grade C/D; and 72.7% of patients met the criteria for high-risk disease.

Of the treated patients, 42 completed treatment and 40 were alive and eligible to enroll in the follow up study on day 100. Of these, 32 patients enrolled and 31 completed the follow up study on day 180. Thirteen patients died during the primary study and 1 patient was lost to follow up and presumed deceased. In the follow up study, 3 patients died and 1 was lost to follow up and presumed deceased. Thirty patients received more than the initial 8 infusions (25 who were partial or mixed responders for continued therapy and 5 patients for aGVHD flare). Among the patients who

achieved PR (n = 21) or MR (n = 2) at day 28 and received continued therapy after day 28, 16 of 21 (76.2%) and 1 of 2 (50%) achieved OR at day 56. At day 100, 19 (90.5%) patients with PR at day 28 who received continued therapy achieved OR (10 CR plus 9 PR). Overall survival was 74.1% (40/54) through day 100 and 68.5% (37/54) at day 180.

Infusions were well tolerated with a low incidence of infusion-related events. Three acute infusion reactions were reported in 3 patients. Two of these patients subsequently discontinued infusions and withdrew from the study due to additional treatment-emergent serious adverse events (somnolence and hyper metabolic syndrome). There was no evidence of ectopic tissue formation in any patient. All patients experienced at least 1 treatment-emergent adverse event (TEAE), with a total of 99 TEAEs reported in 35 patients (64.8%). Many of the common TEAEs (occurring in ≥ 10% of patients were conditions related to SR-aGVHD, infections due to immunosuppressive agents, or steroid toxicities and were not attributed to the study product. A total of 16 TEAEs in 9 patients (17%) were assessed by investigators as possibly related to remestemcel-L-rknd treatment. Ten of these were nonserious and expected in this disease population: decreased neutrophil count, thrombocytopenia, platelet count decreased, cytomegalovirus (CMV) infection, nausea, vomiting, and fever. Six of the possibly related to remestemcel-L-rknd treatment TEAEs reported in 5 patients were serious TEAEs: skin GVHD, adenovirus infection, BK virus infection, hemolytic uremic syndrome, hypermetabolism, and somnolence. Complications of aGVHD and/or relapse were the primary causes of death in the study population.

Remestemcel-L-rknd (Ryoncil®) is considered medically necessary for the treatment of SR-aGVHD in pediatric patients age 2 months and older (≤ 17 years) when the recommended dose of 2 x 10^6 MSCs/kg body weight is administered as an intravenous infusion twice per week for 4 consecutive weeks.
Further treatment with Ryoncil may be considered medically necessary based on assessed treatment response on Day 28 ± 2 after the first infusion as follows:

- Complete response (CR)
  - No further treatment with Ryoncil
- Partial or mixed response*
  - Repeat administration of Ryoncil once a week for additional 4 weeks (4 infusions total)
- No response
  - Consider alternative treatments
- Recurrence of GVHD after CR
  - Repeat administration of Ryoncil twice a week for an additional 4 consecutive weeks (8 infusions total)

Further treatment with Ryoncil, other than as described above, is considered unproven and not medically necessary.

*Partial response is defined as organ improvement of at least one stage without worsening in any other organ. Mixed response is defined as improvement of at least on evaluable organ with worsening in another organ.

Transplant-Associated Thrombotic Microangiopathy

Transplant-associated thrombotic microangiopathy (TA-TMA) is a disease of microvascular endothelial dysfunction and complement activation that can develop following a variety of insults, including inherent predisposition (endothelial dysfunction and complement genetic alterations), toxicity from the hematopoietic cell transplantation (HCT) preparative regimen or graft-versus-host disease (GVHD) prophylaxis, and GVHD itself and infection. These insults result in a proinflammatory, prothrombotic, and proapoptotic milieu in the microvasculature and formation of thrombosis, possibly leading to organ failure. Renal insufficiency and/or failure is the most common organ manifestation of TA-TMA; however, the systemic nature of the pathophysiology can lead to the involvement of other organs, including the central nervous system, lungs and gastrointestinal (GI) system. Clinical manifestations include refractory hypertension, posterior reversible encephalopathy syndrome, seizures, altered mental status, pulmonary hypertension, diffuse alveolar hemorrhage, abdominal pain, GI ischemia and bleeding, and serositis, including pericardial and/or pleural effusions. There are presently no specific diagnostic biomarkers or biomarker panels for TA-TMA. Thus TA-TMA is primarily a clinical diagnosis comprising nonspecific laboratory and clinical manifestations. While a renal biopsy allows for the definitive diagnosis of TA-TMA, this is rarely performed in the post-HCT setting. Furthermore, the kidneys are not always impacted by TA-TMA. Typically an early complication of HCT, TA-TMA is

diagnosed at a median of 22 to 100 days post-HCT. Various therapeutic strategies have been explored for TA-TMA including many complement-targeted agents; however their efficacy has been limited. (Castelli, 2024; Schoettler, 2023; West, 2024).

The lack of harmonization of diagnostic and prognostic indicators has precluded multi-institutional studies to better understand incidence and outcomes. To address this need, the American Society for Transplantation and Cellular Therapy, Center for International Bone Marrow Transplantation, Asia-Pacific Blood and Marrow Transplantation, and European Society for Blood and Marrow Transplantation nominated representatives for an expert panel tasked with reaching consensus on diagnostic and prognostic criteria. The panel reviewed literature, generated consensus statements and identified future directions of investigation. Consensus was reached on four key concepts: (1) TA-TMA can be diagnosed using clinical and laboratory criteria or tissue biopsy of kidney or gastrointestinal tissue; however, biopsy is not required; (2) consensus diagnostic criteria are proposed using the modified Jodele criteria with additional definitions of anemia and thrombocytopenia; (3) risk stratification criteria were developed to identify high-risk patients; and (4) all allogeneic and pediatric autologous HCT recipients with neuroblastoma should be screened weekly for TA-TMA during the first 100 days post-HCT. Patients diagnosed with TA-TMA should be risk-stratified, and those with high-risk disease should be offered participation in a clinical trial for TA-TMA-directed therapy if available (Schoettler, 2023).

In December 2025, the FDA approved narsoplimab-wuug (Yartemlea®) for the treatment of adult and pediatric patients 2 years of age and older with hematopoietic stem cell transplant-associated thrombotic microangiopathy. Yartemlea is a fully human immunoglobulin G4 monoclonal antibody that inhibits mannan-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin pathway of the complement system and represents the first FDA-approved treatment for TA-TMA.

In a single-arm, open label pivotal trial (NCT02222545), patients received intravenous narsoplimab once weekly for 4-8 weeks. The primary end point (response rate) required clinical improvement in two categories: laboratory TMA markers (both platelet count and lactate dehydrogenase) and organ function or freedom from transfusion. Twenty-eight patients (the full analysis set [FAS]) with TA-TMA were enrolled between August 2015 and October 2019 with the last patient completing the study in January 2020. All patients were adults who had undergone allogeneic HSCT. Median age was 48 years (range, 22-68 years) and 71% of patients were male. There were no significant differences in baseline weight or body mass index between patients who received the weight-based dose of 4mg/kg (24 patients) and those who received a fixed dose of 370 mg (four patients). All but one of the patients had a hematologic malignancy. The large majority of patients had multiple risk factors for poor outcomes at baseline, including significant infections, kidney dysfunction, GVHD, neurologic dysfunction, multiple organ TMA involvement, or pulmonary dysfunction. All patients received at least one dose of narsoplimab. The response rate was 61% in the FAS population. Improvement in organ function occurred in 74% of patients in the FAS population. One-hundred-day survival after TA-TMA diagnosis was 68% and 94% in FAS population and responders, respectively, whereas median overall survival was 274 days in the FAS population. The most commonly reported type of adverse event was infection in 71% of patients, including grade 2 or higher infection in 61% of patients. The most common grade 2 or higher infections were cytomegalovirus, lower respiratory tract infection, pneumonia, neutropenic sepsis, Klebsiella pneumoniae infection, septic shock, and staphylococcal bacteremia. Six deaths occurred during the core study period: one patient died of septic shock (3 days after their last narsoplimab dose), two patients each died of progressive acute myeloid leukemia (6 and 40 days after their last dose) and of neutropenic sepsis (14 and 42 days after their last dose), and one patient died of GVHD and TMA (20 days after their last dose). On the basis of follow up data collection, 10 deaths occurred after the study period: three patients died of disease progression; one patient each died of neutropenic sepsis, GVHD/infection, pneumonia, cardiopulmonary arrest; and three patients had unknown cause of death (Khaled, 2022)

Schoettler and colleagues (2025) reported the survival of children (< 16 years old) and adults (≥ 16 years old) enrolled in a global expanded access program (EAP) established to facilitate compassionate use treatment from October 2017 to October 2023 (*n*=136). Inclusion criteria for EAP enrollment included a diagnosis of TA-TMA defined as thrombocytopenia and evidence of microangiopathy. If a patient had any of the following features at TA-TMA diagnosis, they were considered high-risk: sC5b-9 > upper limit of normal (ULN), random urine protein to creatinine

ratio (rUPCR) of ≥ 1mg/mg, Grade 2-4 acute graft-versus-host disease (GVHD) prior to or at any time of TA-TMA diagnosis, organ dysfunction, a lactate dehydrogenase > 2X the ULN, or a bacterial or fungal infection. Among children (*n*=50), the majority underwent allogeneic HCT (*n*=44); 37 were considered high-risk (HR) and 30 (81.1%) had organ dysfunction at the time of TA-TMA diagnosis. One-year overall survival (OS) in pediatric allogeneic recipients with HR TA-TMA who received narsoplimab as first-line therapy (*n*=12) was 75.0% and 56.2% in those who received treatment as ≥ second line (*n*=25, 20 refractory to eculizumab). One-year OS in the six children with solid tumor who underwent autologous HCT was 80%. Among the 86 adults, 84 received an allogeneic HCT, 65 had HR TA-TMA who received narsoplimab as first line therapy (*n*=49) was 58%, and 40.05% in those who received narsoplimab as ≥ second line therapy (*n*=16). There were 113 serious adverse events (SAE) reported in 54 participants. The SAEs reported in > 10% of patients included infections (29 events, 18 patients) and respiratory/mediastinal complications (20 events, 19 patients). Three patients developed meningitis; the organism was reported in one case (enterococcus), but organisms were unknown in the other two cases. All three patients received C5 inhibition prior to narsoplimab.

Narsoplimab-wuug (Yartemlea®) is considered medically necessary for the treatment of adult and pediatric patients 2 years of age and older with hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) when the following criteria are met:

- Biopsy-proven disease (kidney or GI) **OR**
- Meets ≥ 4 of the following 7 criteria within 14 days at 2 consecutive time points
  - Anemia defined as one of the following:
    - Failure to achieve transfusion independence for pRBCs despite evidence of neutrophil engraftment
    - Hemoglobin decline from patient's baseline by 1g/dL
    - New onset of transfusion dependence

      AND
    - Other causes of anemia, such as autoimmune hemolytic anemia (AIHA) and pure red cell aplasia (PRCA), have been ruled out
  - Thrombocytopenia defined as one of the following:
    - Failure to achieve platelet engraftment
    - Higher than expected platelet transfusion needs
    - Refractory to platelet transfusions
    - 50% reduction or greater in baseline platelet count after full platelet engraftment
  - Elevated LDH > ULN for age
  - Presence of schistocytes
  - Hypertension defined as:
    - >99th percentile for age (<18 years) OR
    - Systolic BP ≥ 140 mmHg OR Diastolic BP ≥ 90mmHg (≥ 18years)
  - Elevated sC5b-9 ≥ ULN
  - Proteinuria ≥ 1mg/mg random protein to creatinine ratio (rUPCR)

Approval for treatment beyond the initial 6-month certification period is based on continued evidence of active TA TMA and/or evidence of an inadequate or incomplete response based on Jodele criteria.

The recommended dosage of Yartemlea in adults and pediatric patients two years of age and older is as follows:

Weight (kg)	Recommended Dosage
Greater than or equal to 50 kg	370 mg given as an intravenous infusion over 30 minutes once weekly. Increase frequency to twice weekly if there is inadequate improvement in TA-TMA signs and symptoms.
Less than 50 kg	4 mg/kg given as an intravenous infusion over 30 minutes once weekly. Increase frequency to twice weekly if there is inadequate improvement in TA-TMA signs and symptoms.

Source: FDA Full Prescribing Information; narsoplimab-wuug (Yartemlea®). December 2025.

Veno-Occlusive Disease (VOD)

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.

Transplant Consultation Timing Guideline

The National Marrow Donor Program (NMDP [SM]) 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: New website: Disease-Specific Hematopoietic Cell transplant (HCT) Indications and Outcomes Data | NMDP

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]. Transplant consultation may be reasonable for favorable-risk AML patients with unusual or adverse co-mutations or cytogenetic alterations. Early referral for allogeneic HCT should also be considered for any AML patients in CR1 who are 60 years old or older; regardless of cytogenetic or genomic information.
- Antecedent hematological disease (e.g., myelodysplastic syndrome [MDS]), either based on prior clinical diagnosis or suggested by the presence of secondary-type somatic mutations on molecular testing
- 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 and referral to HCT consultation is recommended at diagnosis for all patients with:

- 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 primary myelofibrosis (PMF) and essential thrombocytopenia or polycythemia vera that has progressed to MF (secondary MF).
High-resolution HLA typing and referral to HCT consultation is recommended at diagnosis for all patients with:

- DIPSS or DIPSS Plus Intermediate-1 (INT-1) or higher
- MIPSS70/MIPSS 70 plus version 2.0 intermediate-risk or higher
- Cytopenic subtype
- Young age
- High-risk features including high-risk mutations (ASXL1, TP53), triple negative (lack of a driver mutation such as JAK2, MPL or CALR)
- Patients failing JAK inhibitor therapy

HCT is recommended upfront for patients with:

- DIPSS or DIPSS Plus Intermediate-2 (INT-2) and high-risk disease
- MIPSS70/MIPSS 70 plus version 2.0 high-risk disease
- Patients with DIPSS INT-1 or MIPSS70/MIPSS 70 plus version 2.0 intermediate-risk, cytopenic subtype, young age, high-risk features, including high-risk mutations (ASXL1, TP53), triple negative (lack of a driver mutation such as JAK2, MPL, or CALR) and those failing JAK inhibitor therapy should be considered for upfront HCT balancing patient preferences and clinical trial options

Chronic Lymphocytic Leukemia (CLL)

- Resistance or intolerance to BTK inhibitors and/or BCL2 inhibitors
- Ritcher's transformation

Pediatric Acute 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 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 ≤ 39 years)

- Infant at diagnosis
  - Unfavorable genetics
  - Age < 3 months with any WBC, or < 6 months with WBC > 300,000 at presentation or any infant with measurable (also known as minimal) residual disease (MRD)+ after consolidation
- Primary induction failure (M3 marrow) after achieving MRD negative status
- Presence of MRD after initial therapy; MRD ≥ 0.01% following consolidation (9–12 weeks from diagnosis)
- High/very high-risk CR1, including:

  - Philadelphia chromosome positive slow-TKI responders or with *IKZF*1 deletions; Philadelphia-like if MRD+ at end of consolidation, or persistently detectable low level of molecular disease
  - *iAMP*21 if MRD+ at end of consolidation
  - 11q23 rearrangement if MRD+ at end of consolidation
- First relapse with aim to transplant in CR2
- CR2 and beyond, if not previously evaluated, including:
  - all young adults in CR2
  - early relapse (≤36 months from diagnosis for medullary disease, ≤18 months from diagnosis for EMD)
  - MRD+ (>0.1% for medullary disease or equivalent for EMD) after re-induction (4–8 weeks from relapse)
  - T cell ALL
  - CR3 and beyond
- Chimeric Antigen Receptor Therapy (CAR-T), including:
  - patients who receive CD19 4-1BB and achieve MRD negative CR if they have not already received HCT
  - patients who receive CD22 or other investigational therapies

Myelodysplastic Syndromes (MDS)

- At diagnosis for all subtypes

Juvenile Myelomonocytic Leukemia (JMML)

- At diagnosis

Lymphomas

Non-Hodgkin Lymphoma

Follicular (FL)

- Poor response to initial treatment
- Initial remission duration < 24 months
- At relapse (CAR or allo HCT can be offered to patients with multiple relapsed FL)
- 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

Hodgkin Lymphoma

- Primary refractory disease
- First or subsequent relapse
- Brentuximab vedotin and check point inhibitor refractory and/or intolerant disease (for allo HCT)

Other Malignant Diseases

Germ Cell Tumors

High-dose therapy with autologous stem cell support may be considered for patients with:

- Non-germinomatous germ cell tumors (NGGCTs) for refractory disease post induction chemotherapy as long as the patient has chemo-responsive disease and does not have bulky residual tumor
- Germinoma or NGGCT if the patient has chemo-responsive disease to reinduction chemotherapy and does not have bulky residual tumor

Neuroblastoma

- INRGSS L2 at diagnosis
  - *MYCN* amplification
  - age > 18 months with unfavorable histology and segmental chromosome aberration
- INRGSS stage M at diagnosis
  - *MYCN* amplification
  - age > 18 months at diagnosis
  - age 12-18 months with unfavorable histology, segmental chromosome aberrations, or diploid DNA content

Ewing family of tumors

- Metastatic disease at diagnosis
- First relapse or CR 2

Medulloblastoma

High-dose therapy with autologous stem cell support may be considered standard therapy for several infant (younger than 3 years of age) embryonal tumors as first line, including:

- Medulloblastoma
- Atypical teratoid rhabdoid tumor (AT/RT)
- Embryonal tumor with multilayered rosettes (ETMR)
- Primitive neuroectodermal/embryonal tumors, not otherwise specified (NOS)

High-dose therapy with autologous stem cell support may be considered at relapse for patients with:

- Embryonal tumors as long as the patient has chemoresponsive disease to re-induction chemotherapy and does not have bulky residual disease

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

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
- Adreno leukodystrophy (ALD): following the diagnosis of the cerebral form of ALD

Hemoglobinopathies

Sickle Cell Disease

- Children (especially under age 13) with available matched sibling donors
- 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
  - Abnormal transcranial Doppler (TCD) velocity of ≥ 200 cm/sec or > 185 cm/sec with intracranial vasculopathy
  - Frequent episodes of acute chest syndrome or severe vaso-occlusive pain crises or combination of both in the preceding 2–3 years
  - Regular red blood cell transfusions to prevent sickle cell disease complications
  - Tricuspid valve regurgitant jet (TRJ) velocity ≥ 2.7 m/sec (mainly in adults)
  - Chronic pain ≥ 6 months (leg ulcers, avascular necrosis)

Transfusion-dependent Thalassemias

- At diagnosis

Hemophagocytic Lymphohistiocytosis (HLH)

- At diagnosis

Other Marrow Failure Syndromes

Including Diamond-Blackfan anemia, Shwachman-Diamond syndrome, Fanconi anemia, Dyskeratosis Congenita and others.

- Diamond-Blackfan Anemia: continued transfusion dependent anemia following a course of steroid therapy, development of significant infections, MDS/AML
- Shwachman-Diamond syndrome, Fanconi anemia, Dyskeratosis Congentia and others: development of cytopenias, transfusion dependence, or significant infections; high-risk cytopenic clones, high-risk somatic mutation patterns; MDS/AML

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: Risk Classification by Genetics at Initial AML Diagnosis

Risk category	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 †,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 †,‡ • Mutated NPM1†,§ without FLT3-ITD • bZIP in-frame mutated CEBPAk
Intermediate	• Mutated NPM1†,§ with FLT3-ITD • Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/DEK::NUP214 • t(v;11q23.3)/KMT2A-rearranged # • t(9;22)(q34.1;q11.2)/BCR::ABL1 • t(8;16)(p11.2;p13.3)/KAT6A::CREBBP • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1) • t(3q26.2;v)/MECOM(EVI1)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,** monosomal karyotype †† • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡ • Mutated TP53 [a]

*Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

†Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.

‡Concurrent KIT and/or FLT3 gene mutation does not alter risk categorization.

§AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.

ııOnly in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.

¶The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse risk gene mutations.

#Excluding KMT2A partial tandem duplication (PTD).

**Complex karyotype: $3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.

††Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).

‡‡For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

[a]TP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Source: Dohner H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. doi: 10.1182/blood.2022016867.

Appendix B: Prognostic Risk Scores for Myelodysplastic Syndrome

Medicare coverage for allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with MDS are dependent on prognostic risk scores of:

- ≥ 1.5 (Intermediate-2 or high) using the International Prognostic Scoring System (IPSS), or
- ≥ 4.5 (high or very high) using the International Prognostic Scoring System - Revised (IPSS-R), or
- ≥ 0.5 (high or very high) using the Molecular International Prognostic Scoring System (IPSS-M)

https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=366

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
Peripheral blood blasts ≥ 1%	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 109/L	1
RBC transfusion need	1

*Adverse karyotypes include +8, -5/del5q, -7/del7qi(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).

Source: Gagelmann N, Ditschkowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. Blood. 2019 May 16;133(20):2233-2242. doi: 10.1182/blood-2018-12-890889. Epub 2019 Feb 13. PMID: 30760453.

Appendix D: 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.

Source: Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022 Aug;97(8):1086-1107. doi: 10.1002/ajh.26590. Epub 2022 May 23. PMID: 35560063; PMCID: PMC9387011

Appendix E: 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 F: 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.
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Gale Encyclopedia of Medicine. Copyright 2008 The Gale Group, Inc. All rights reserved.
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Appendix G: Expanded Disability Status Scale (EDSS)

The expanded disability status scale (EDSS) is the most commonly used scale in patients with MS. EDSS is a very effective method in reflecting disability. EDSS assessment is a non-linear assessment and is a scale in which MS is evaluated between 0 and 10, where normal neurological examination is 0 and MS-related death is 10.

Score	Criteria
0	Normal neurological exam (all grades 0 in Functional Systems [FS]; cerebral grade 1 acceptable)
1.0	No disability, minimal signs in one FS (i.e., grade 1, excluding cerebral grade 1)
1.5	No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some twelve hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 500 meters.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, characterized by relatively severe disability, usually consisting of one FS grade 4 (others grade 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.
5.0	Ambulatory without aid or rest for some 200 meters; disability severe enough to impair full daily activities (e.g. to work a full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).
6.5	Constant bilateral assistance (cane, crutch, or brace) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).
7.0	Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some

	12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone).
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+).
8.0	Essentially restricted to bed or chair or perambulated in wheelchair; but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5	Essentially restricted to bed much of the day; has some effective use of the arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally grade 4+ in several systems).
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+ in several systems).
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+).
10	Death due to MS.

Source: Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale. Neurology 1983; 33: 1444-1452

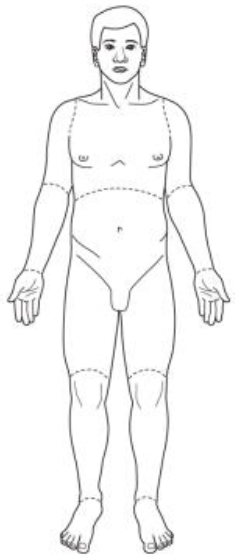
Appendix H: modified Rodnan Skin Thickness Score (mRSS)

The mRSS is a 17-site assessment instrument to quantify the thickness of the skin and the extent of involvement in SSc. The skin is assessed by palpation and graded based on its thickness/mobility between 0 to 3, where 0 is normal skin and 3 is very thick and immobile skin. It is the most commonly used method for assessing skin involvement in SSc patients.

Modified Rodnan Skin Score (MRSS) Document

Subject ID: _____

Date of Examination: _____



	Right				Left			
Fingers	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Hands	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Forearms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Upper Arms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Face			0☐	1☐	2☐	3☐		
Anterior Chest			0☐	1☐	2☐	3☐		
Abdomen			0☐	1☐	2☐	3☐		
Thighs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Legs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Feet	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Column Totals								
Total:								

Key: *0 – No Thickening* *1 – Mild Thickening* *2 – Moderate Thickening* *3 – Severe Thickening*

Notes:

Examiner:

Printed Name: _____

Signature: _____ Date: _____

Source: Desai R, Chawla H, Larin K, Assassi S. Methods for objective assessment of skin involvement in systemic sclerosis. Curr Opin Rheumatol. 2023 Nov 1;35(6):301-308. doi: 10.1097/BOR.0000000000000968. Epub 2023 Aug 21. PMID: 37605869; PMCID: PMC11015902.

Appendix I: 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. **Note:** 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-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.

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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.

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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.

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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 J: MAGIC Criteria: Acute GVHD Target Organ Staging & Overall Clinical Grade

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25%-50% BSA	3.1-6mg/dL		Adult: 1000-1500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15mg/dL		Adult: >1500 mL/day or > 7 episodes/day Child: >30 mL/kg/day or > 10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Grade (based on most severe target organ involvement)	
0	No stage 1-4 of any organ
I	Stage 1-2 skin without liver, upper GI or lower GI involvement
II	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
III	Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI
IV	Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI
0	No stage 1-4 of any organ

Source: Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2016 Jan;22(1):4-10. doi: 10.1016/j.bbmt.2015.09.001. Epub 2015 Sep 16. PMID: 26386318; PMCID: PMC4706482.

Appendix K: Hematopoietic Stem Cell Transplant Quick Reference Guide

This appendix is to be used solely as a quick reference guide to identify standard of care. This guide does not reflect potential exceptions such as enrollment in a clinical trial. It is required that the user read the guideline for important criteria and directions concerning medical director escalation.

Disease/Indication	Autologous	Allogeneic
Leukemias		
Acute Lymphoblastic Leukemia (ALL)	Yes	Yes
Acute myeloid leukemia (AML)	Yes	Yes
Chronic lymphocytic leukemia (CLL)	No	Yes
Chronic myeloid leukemia (CML)	No	Yes
Prolymphocytic leukemia	Yes	Yes
Myelodysplastic Syndromes & Mixed Myelodysplastic/Myeloproliferative Neoplasms		
Myelodysplastic syndromes (MDS)	No	Yes
Juvenile myelomonocytic leukemia (JMML/JCML)	No	Yes
Chronic myelomonocytic leukemia (CMML)	No	Yes
Myeloproliferative Disorders		
Primary myelofibrosis and related conditions	No	Yes
Secondary myelofibrosis	No	Yes
Brain Tumors		
Anaplastic astrocytoma	No	No
Brain stem glioma	No	No
Ependymoma	No	No
Germinoma	No	No
Glioblastoma Multiforme (GBM)	No	No
Medulloblastoma	Yes	No

Oligodendroglioma	Yes	No
Pineoblastoma	Yes	No
Embryonal Tumors with Multi-layered Rosettes (ETMR). Formerly known as Primitive Neuroectodermal Tumor (PNET)	Yes	No
Disease/Indication	**Autologous**	**Allogeneic**
Germ Cell Tumors		
Testicular germ cell tumor	Yes	No
Extragonadal germ cell tumor	Yes	No
Seminoma	Yes	No
Choriocarcinoma	Yes	No
Embryonal carcinoma	Yes	No
Mixed germ cell tumors	Yes	No
Teratoma	Yes	No
Yolk-sac tumor (endodermal sinus tumor)	Yes	No
Germ cell tumor of the ovary	Yes	No
Multiple Myeloma/ Plasma Cell Disorders		
Multiple Myeloma		
Single Auto	Yes	No
Tandem (auto followed by auto)	Yes	No
Tandem (auto followed by allo)	Yes	No
Allogenic	No	Yes
AL-Amyloidosis	Yes	No
Waldenstrom macroglobulinemia	Yes	Yes
Monoclonal gammopathy of renal significance (MGRS)	Yes	No
Monoclonal gammopathy of uncertain significance (MGUS)	No	No
Polyneuropathy organomegaly endocrinopathy, monoclonal gammopathy skin defects syndrome (POEMS)	Yes	No
Solitary Plasmacytoma	No	No

Hodgkin Lymphoma		
Hodgkin Lymphoma	Yes	Yes
Disease/Indication	**Autologous**	**Allogeneic**
Non-Hodgkin Lymphoma (NHL)		
Small B-cell lymphocytic lymphoma	No	Yes
Follicular lymphoma	Yes	Yes
Lymphoplasmacytoid lymphoma/immunocytoma	Yes	Yes
Marginal zone lymphoma (mucosa-associated lymphoid tissue, splenic, nodal)	Yes	Yes
Burkitt lymphoma	Yes	Yes
Diffuse, large cell lymphoma (mediastinal large cell, primary effusion)	Yes	Yes
Mantle cell lymphoma	Yes	Yes
Precursor B-cell leukemia/lymphoma	Yes	Yes
T-cell Lymphoma	Yes	Yes
Other Malignancies		
Atypical teratoid rhabdoid tumors	Yes	No
Blastic plasmacytoid dendritic cell neoplasm	No	Yes
Epithelial ovarian cancer	No	No
Ewing tumor (Ewing sarcoma)	Yes	No
Neuroblastoma	Yes	No
Osteogenic sarcoma	No	No
Renal cell carcinoma	No	No
Retinoblastoma	Yes	No
Rhabdomyosarcoma/soft tissue sarcoma	No	No
Supratentorial ependymoma	Yes	No
Wilms tumor	Yes	No

Hematological Disorders	Autologous	Allogeneic
Aplastic Anemia	No	Yes
Blackfan-Diamond Syndrome	No	Yes
Chronic Granulomatous Disease	No	Yes
Congenital Agranulocytosis (Kostmann Syndrome)	No	Yes
Congenital Amegakaryocytic Thrombocytopenia	No	Yes
Dyskeratosis Congenita	No	Yes
Fanconi Anemia	No	Yes
Paroxysmal Nocturnal Hemoglobinuria (PNH)	No	Yes
Shwachman-Diamond Syndrome	No	Yes
Sickle Cell Disease (SCD)	No	Yes
Thalassemia Major	No	Yes
Immunodeficiency Syndromes		
CD40 ligand deficiency	No	Yes
Chediak-Higashi syndrome	No	Yes
Hemophagocytic Lymphohistiocytosis (HLH) (same as familial Erythrophagocytic lymphohistiocytosis - FEL)	No	Yes
Leukocyte adhesion deficiency	No	Yes
Omenn syndrome	No	Yes
Severe Combined Immunodeficiency Disease (SCID)	No	Yes
Wiskott-Aldrich syndrome	No	Yes
X-linked lymphoproliferative syndrome	No	Yes
Gaucher disease type 1	No	Yes
Niemann-Pick type B	No	Yes
Fucosidosis	No	Yes
Lysosomal storage diseases	No	Yes

Autoimmune Diseases		
Crohn’s disease	No	No
Multiple sclerosis	Yes	No
Rheumatoid arthritis	No	No
Systemic lupus erythematosus (SLE)	No	No
Systemic sclerosis (Scleroderma)	Yes	No
Inherited Metabolic Disorders		
Adrenoleukodystrophy	No	Yes
Epidermolysis bullosa	No	Yes
Globoid cell leukodystrophy (Krabbe Disease)	No	Yes
Hurler syndrome (MPS I)	No	Yes
Hunter syndrome (MPS II)	No	Yes
Mannosidosis	No	Yes
Maroteaux-Lamy Syndrome (MPS VI)	No	Yes
Metachromatic leukodystrophy	No	Yes
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	No	Yes
Osteopetrosis	No	Yes
Rett syndrome	No	Yes
Cardiac Conditions		
Heart disease	No	No

Review and Approval History

Version	Date and Description
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	**10/10/2013:** Revised and updated. Approved by Medical Technology Assessment Committee
2.0	**10/16/2013:** Approved by Complex Medical Conditions Policy Committee
2.0	**11/12/2013:** 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	**08/25/2015:** 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
6.0	**06/22/2017:** 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	**11/01/2017:** Updated to reflect FDA-approval of new CAR-T Therapy agent axicabtagene ciloleucel (Yescarta™)
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	**04/17/2019:** 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	**12/02/2019:** Corrected follicular lymphoma indication on page 10. Updated supporting references.
10.0	**06/10/2020:** 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	**08/06/2020:** Approved by Medical Technology Assessment Committee
10.0	**08/11/2020:** Presented to National Medical Care Management Committee
10.0	**11/11/2020**: Updated minimal/measurable disease terminology
11.0	**06/15/2021:** Annual Review with Optum Stem Cell Transplantation Expert Panel. No revisions.
11.0	**09/09/2021:** Approved by Medical Technology Assessment Committee
11.0	**09/14/2021:** Presented to National Medical Care Management Committee
12.0	**07/29/2022:** 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	**09/01/2022:** Approved by Medical Technology Assessment Committee
12.0	**09/08/2022:** Presented to National Medical Care Management Committee
12.0	**01/05/2023:** Interim update. Added criteria for autologous HSCT in patients with monoclonal gammopathy of renal significance (MGRS). Approved by Medical Technology Assessment Committee.
12.0	**01/10/2023:** Presented to National Medical Care Management Committee
13.0	**07/12/2023:** 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 onlv; updated NMDP/ASBMT Recommended Timing for Stem Cell Transplantation Consultation.
13.0	**09/11/2023:** Approved by Optum Clinical Guideline Advisory Committee
13.0	**10/05/2023:** Approved by Medical Technology Assessment Committee
13.0	**11/08/2023:** Approved by the Medicare Advantage Policy -Technology Advisory Committee (MAP-TAC)
13.0	**11/17/2023:** Approved by the Pharmacy and Therapeutics (P&T) Committee
14.0	**08/28/2024:** Annual review with Optum Hematopoietic Stem Cell Transplant and Chimeric Antigen Receptor T-Cell Therapy Expert Panel . Guideline reformatted. Updated NMDP/ASTCT Recommended Timing for Transplant Consultation.
14.0	**10/09/2024:** Approved by Optum Clinical Guideline Advisory Committee
14.0	**11/07/2024:** Approved by Medical Technology Assessment Committee
14.0	**04/11/2025:** Interim update: added literature review and medical necessity criteria for Remestemcel-L-rknd (Ryoncil®); updated NMDP Transplant Consultation Timing Guideline. Approved by Optum Clinical Guideline Advisory Committee.

14.0	**05/01/2025:** Interim update approved by Medical Technology Assessment Committee.
14.0	**05/16/2025:** Interim update approved by Pharmacy and Therapeutics (P&T) Committee.
15.0	**05/21/2025:** Annual review with Optum Stem Cell Transplantation and Chimeric Antigen Receptor T-cell Therapy Expert Panel.
15.0	**06/11/2025:** Annual review; no changes. Approved by Optum Clinical Guideline Advisory Committee.
15.0	**07/10/2025:** Annual review; no changes. Approved by Medical Technology Assessment Committee.
15.0	**07/16/2025:** Annual review; no changes. Approved by the Pharmacy and Therapeutics (P&T) Committee.
15.0	**03/09/2026:** Interim revision: • Omidubicel onlv (Omisirge®): new indication for use in adults and pediatric patients 6 years and older with severe aplastic anemia following reduced intensity conditioning. Approved by Optum Clinical Guideline Advisory Committee.
15.0	**03/18/2026:** Interim revision: • Omidubicel onlv (Omisirge®): new indication for use in adults and pediatric patients 6 years and older with severe aplastic anemia following reduced intensity conditioning. Approved by Pharmacy and Therapeutics (P&T) Committee.
15.0	**04/02/2026:** Interim revision: • Omidubicel onlv (Omisirge®): new indication for use in adults and pediatric patients 6 years and older with severe aplastic anemia following reduced intensity conditioning. Approved by Medical Technology Assessment Committee (MTAC).
15.0	**04/08/2026:** Interim revision: • Omidubicel onlv (Omisirge®): new indication for use in adults and pediatric patients 6 years and older with severe aplastic anemia following reduced intensity conditioning. Approved by Medicare Advantage Policy and Technology Assessment Committee (MAP TAC).
16.0	**04/22/2026:** Annual review by the Optum Hematopoietic Stem Cell Transplantation and Chimeric Antigen Receptor T-Cell Therapy Expert Panel.
16.0	**05/11/2026: Annual review:** • Acute Lymphoblastic Leukemia (ALL) – criteria for allogeneic stem cell transplant updated • Acute Myeloid Leukemia (AML) – criteria for allogeneic stem cell transplant updated and new appendix added • Donor lymphocyte infusion (DLI) criteria updated for clarity • Multiple sclerosis - medical necessity criteria for autologous stem cell transplant updated and new appendix added • Systemic sclerosis – medical necessity criteria for autologous stem cell transplant updated and new appendix added • Narsoplimab-wuug (Yartemlea) – new treatment for hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) Approved by Optum Clinical Guideline Advisory Committee.
16.0	**05/15/2026: Annual review:** • Acute Lymphoblastic Leukemia (ALL) – criteria for allogeneic stem cell transplant updated • Acute Myeloid Leukemia (AML) – criteria for allogeneic stem cell transplant updated and new appendix added • Donor lymphocyte infusion (DLI) criteria updated for clarity

	• Multiple sclerosis - medical necessity criteria for autologous stem cell transplant updated and new appendix added • Systemic sclerosis – medical necessity criteria for autologous stem cell transplant updated and new appendix added • Narsoplimab-wuug (Yartemlea) – new treatment for hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) Approved by Pharmacy and Therapeutics (P&T) Committee.
16.0	**06/04/2026: Annual review:** • Acute Lymphoblastic Leukemia (ALL) – criteria for allogeneic stem cell transplant updated • Acute Myeloid Leukemia (AML) – criteria for allogeneic stem cell transplant updated and new appendix added • Donor lymphocyte infusion (DLI) criteria updated for clarity • Multiple sclerosis - medical necessity criteria for autologous stem cell transplant updated and new appendix added • Systemic sclerosis – medical necessity criteria for autologous stem cell transplant updated and new appendix added • Narsoplimab-wuug (Yartemlea) – new treatment for hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) Approved by Medical Technology Assessment Committee (MTAC).
16.0	**06/10/2026: Annual review:** • Acute Lymphoblastic Leukemia (ALL) – criteria for allogeneic stem cell transplant updated • Acute Myeloid Leukemia (AML) – criteria for allogeneic stem cell transplant updated and new appendix added • Donor lymphocyte infusion (DLI) criteria updated for clarity • Multiple sclerosis - medical necessity criteria for autologous stem cell transplant updated and new appendix added • Systemic sclerosis – medical necessity criteria for autologous stem cell transplant updated and new appendix added • Narsoplimab-wuug (Yartemlea) – new treatment for hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) Approved by Medicare Advantage Policy and Technology Assessment Committee (MAP TAC).