

# Medical Policy

<b>Subject:</b>	Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome	<b>Publish Date:</b>	01/30/2025
<b>Document#:</b>	TRANS.00024	<b>Last Review Date:</b>	11/14/2024
<b>Status:</b>	Revised		

## Description/Scope

This document addresses hematopoietic stem cell transplantation (HSCT) or hematopoietic cell transplant (HCT) in the treatment of the following select leukemias and myelodysplastic disorders:

- Acute Myeloid Leukemia (AML)
- Acute Lymphoblastic Leukemia (ALL)
- Chronic Myeloid Leukemia (CML)
- Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
- Chronic Myelomonocytic Leukemia (CMML), Myelodysplastic Syndrome (MDS), Myeloproliferative Neoplasms (MPN)
- Myelofibrosis

**Note:** For additional stem cell transplant information and criteria, see the applicable transplant document:

- MED.00147 Cellular Therapy Products for Allogeneic Stem Cell Transplantation
- TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation
- TRANS.00023 Hematopoietic Stem Cell Transplantation for Multiple Myeloma and Other Plasma Cell Dyscrasias
- TRANS.00028 Hematopoietic Stem Cell Transplantation for Hodgkin Disease and non-Hodgkin Lymphoma

## Position Statement

### I. *Acute Myeloid Leukemia (AML)*

#### Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **medically necessary** for individuals with AML in any phase of illness after induction when *none* of the following indicators of a favorable AML classification are present:
1. Core binding factor (CBF) AML [inv(16) or t(8;21)] with unmutated (wild-type) C-Kit; **or**
  2. Acute promyelocytic leukemia (APL) t(15;17) in first complete remission; **or**
  3. Cytogenetically normal AML with FLT3-ITD non-mutated (wild-type) and NPM1 mutated.
- B. *A repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary**.

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- C. A second or repeat allogeneic (ablative or non-myeloablative) stem cell transplantation due to relapsed disease is considered **medically necessary**.

### Investigational and Not Medically Necessary:

- A. Allogeneic (ablative or non-myeloablative) stem cell transplantation is considered **investigational and not medically necessary** for individuals with AML when any of the following indicators of a favorable classification are present:
1. Core binding factor (CBF) AML [inv(16), t(8;21)] with unmutated (wild-type) C-Kit; **or**
  2. Acute promyelocytic leukemia (APL) t(15;17) in first complete remission; **or**
  3. Cytogenetically normal AML with FLT3-ITD non mutated (wild-type) and NPM1 mutated.
- B. Autologous stem cell transplantation is considered **investigational and not medically necessary** for individuals with AML.
- C. A second or repeat allogeneic (ablative or non-myeloablative) transplant due to persistent or progressive disease is considered **investigational and not medically necessary**.
- D. Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary**.

## II. Acute Lymphoblastic Leukemia (ALL)

**Note:** There is no clear age cut-off that distinguishes adult from childhood ALL. Published data generally group outcomes according to whether the individual is treated by an adult or pediatric oncologist.

### Medically Necessary:

- A. Allogeneic (ablative or non-myeloablative) stem cell transplantation is considered **medically necessary** provided the individual has a diagnosis of ALL and **one** of the following:
1. Individual is in **first complete remission** and has **one or more** of the following "high-risk" factors:
    - a. Philadelphia chromosome positive [t(9;22) or BCR-ABL positive];
    - b. Any of the following cytogenetic or molecular abnormalities: t(4;11), t(1;19), t(8;14), del(7q), trisomy 8, 11q23 (MLL) translocation;
    - c. Hypodiploidy (less than 44 chromosomes);
    - d. B-cell immunophenotype;
    - e. Age greater than 15 years;
    - f. Leukocyte count greater than  $50 \times 10^9/L$ ;
    - g. Extramedullary disease (especially central nervous system);
    - h. Failure to achieve a complete remission within 6 weeks of the start of induction therapy;
    - i. Minimal residual disease (MRD) positivity following induction;
- or**

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2. Individual is in **second or subsequent complete remission; or**
3. Individual is in **any relapse.**

- B. *A repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary.**

### Investigational and Not Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **investigational and not medically necessary** for individuals who do not meet the above criteria.
- B. *A second or repeat allogeneic (ablative or non-myeloablative) transplant* due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary.**
- C. Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary.**
- D. *Autologous stem cell transplant* is considered **investigational and not medically necessary** for individuals with ALL.

### III. Chronic Myeloid Leukemia (CML)

#### Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **medically necessary** for individuals with CML and **any** of the following indications:
  1. No hematologic response at 3 months; **or**
  2. No cytogenetic response at 6 months; **or**
  3. Cytogenetic relapse at 12 or 18 months after achieving initial hematologic remission; **or**
  4. Partial cytogenetic response at 18 months; **or**
  5. Individuals with T315-I mutation; **or**
  6. Individuals in accelerated or blast phase.
- B. *An allogeneic stem cell transplantation (ablative or non-myeloablative) after a prior autologous stem cell transplantation* is considered **medically necessary** for individuals who meet the above criteria.

**Note:** This applies if a previous autologous transplant was performed, regardless if the Position Statement deems autologous stem cell transplantation as **investigational and not medically necessary.**

- C. *A repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary.**

#### Investigational and Not Medically Necessary:

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- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **investigational and not medically necessary** for individuals who do not meet the above criteria.
- B. *Autologous stem cell transplantation* is considered **investigational and not medically necessary**.
- C. *A second or repeat allogeneic (ablative or non-myeloablative) transplant* due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary**.
- D. Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary**.

### IV. *Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)*

#### Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **medically necessary** for individuals with CLL or SLL who are refractory to small molecule inhibitor therapy.
- B. *An allogeneic stem cell transplantation (ablative or non-myeloablative) after a prior autologous stem cell transplantation\** is considered **medically necessary** for individuals with CLL or SLL who meet the above criteria.

**\*Note:** This applies if a previous autologous transplant was performed, regardless if the Position Statement deems autologous stem cell transplantation as **investigational and not medically necessary**.

- C. *A repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary**.

#### Investigational and Not Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **investigational and not medically necessary** for individuals with CLL or SLL who do not meet the above criteria.
- B. *Autologous stem cell transplantation in individuals* with CLL or SLL is considered **investigational and not medically necessary**.
- C. *A second or repeat allogeneic (ablative or non-myeloablative) transplant* due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary**.
- D. Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary**.

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## V. *Myelodysplastic Syndromes (MDS) including Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN)*

### Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **medically necessary** for individuals who have chronic myelomonocytic leukemia (CMML) or a *de novo or primary* myelodysplastic syndrome with an intermediate International Prognostic Scoring System (IPSS) score of 1.5-2.0 or a high IPSS score of greater than or equal to 2.5 or a Revised IPSS (IPSS-R) intermediate score of greater than 3.5 or a high or very high IPSS-R score. Individuals may have the allogeneic transplant as initial therapy.\*
- B. *Allogeneic (ablative and non-myeloablative) stem cell transplantation* is considered **medically necessary** for individuals who have a myelodysplastic syndrome with a low or intermediate IPSS of 0-1.0 or an IPSS-R of 3.5 or less who have not responded to prior therapy.\*

**\*Note:** An IPSS is not required for the treatment of de novo or primary myelodysplastic syndrome or juvenile myelomonocytic leukemia (JMML) in the pediatric population.

- C. *Allogeneic (ablative and non-myeloablative) stem cell transplantation* is considered **medically necessary** for individuals who have *secondary* myelodysplastic syndrome.
- D. *An allogeneic stem cell transplantation (ablative or non-myeloablative) after a prior autologous stem cell transplantation* is considered **medically necessary** for individuals who meet the above criteria.

**Note:** This applies if a previous autologous transplant was performed, regardless if the Position Statement deems autologous stem cell transplantation as **investigational and not medically necessary**.

- E. *A repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary**.

### Investigational and Not Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **investigational and not medically necessary** for individuals who do not meet the above criteria.
- B. *Autologous stem cell transplantation* in individuals with CMML, MDS or myeloproliferative neoplasms is considered **investigational and not medically necessary**.
- C. *Allogeneic (ablative and non-myeloablative) stem cell transplantation* is considered **investigational and not medically necessary** in individuals with the following myeloproliferative neoplasms (MPN): polycythemia vera, essential thrombocytopenia).

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- D. *A second or repeat allogeneic (ablative or non-myeloablative) transplant* due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary**.
- E. Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary**.

## VI. Myelofibrosis

### Medically Necessary:

- A. *Allogeneic (ablative or non-myeloablative) stem cell transplantation* is considered **medically necessary** in individuals with myelofibrosis.
- B. *An allogeneic stem cell transplantation (ablative or non-myeloablative) after a prior autologous stem cell transplantation* is considered **medically necessary**.

**Note:** This applies if a previous autologous transplant was performed, regardless if the Position Statement deems autologous stem cell transplantation as **investigational and not medically necessary**.

- C. *A repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary**.

### Investigational and Not Medically Necessary:

- A. *Autologous stem cell transplantation* in individuals with myelofibrosis is considered **investigational and not medically necessary**.
- B. *A second or repeat allogeneic (ablative or non-myeloablative) transplant* due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary**.
- C. Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary**.

## Rationale

### AML

The World Health Organization (WHO) incorporates multiple features into their classification system including morphology, cytogenetic, molecular genetics and immunologic markers in order to provide a universally applicable and prognostically valid tool (National Cancer Institute [NCI], 2023). This classification system facilitates identifying individuals that may have better response to therapies. There is ongoing prognostic and diagnostic research to identify cytogenetic markers and to correlate this information with appropriate treatment modalities. Individuals with higher risk of relapse based on the prognostic indicators typically receive more aggressive

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therapies. Analysis of clinical trial data has shown individuals with favorable cytogenetics have improved 5-year survival rates when compared to those with intermediate- and poor/adverse-risk cytogenetics. Cytogenetic and molecular abnormalities that are classified as “favorable” indicate a good prognosis and include t(8;21); inv(16;16); t(15;17); and a single nucleophosmin mutation (NPM1) with normal karyotype. Poor prognosis with chemotherapy are associated with monosomies of chromosomes 5 or 7; c-kit mutations; by translocations or inversions of chromosome 3; t(6;9); t(9;22); isolated FLT3-ITD (internal-tandem duplications); or by abnormalities of chromosome 11q23 (National Comprehensive Cancer Network® [NCCN], V3. 2024; NCI, 2024). According to NCCN, individuals with treatment-related AML, prior MDS or those requiring two or more inductions to achieve complete response are at increased risk for relapse and are considered high-risk. Overall survival (OS) and leukemia-free survival were negatively impacted in the presence of del(9q) in a French Collaborative Study (Prebet, 2009). In clinical trials, individuals with good-risk cytogenetics t(8;21) and inv(16) demonstrated increased relapse rates when c-kit mutations were also present compared to individuals with wild-type c-kit.

In individuals in first complete remission (CR1), allogeneic HSCT has been shown to decrease the leukemic relapse rate, but at the price of increased treatment-related morbidity and mortality. This raises the question of whether allogeneic transplant offers any real benefit as a post-remission strategy in individuals in CR1. Furthermore, it is unclear whether the outcomes associated with high-dose therapy are better compared to those associated with other non-marrow ablative dose-intensification strategies, such as high-dose cytarabine. At the present time, high-dose chemotherapy with allogeneic stem cell support is typically reserved for those with high risk or intermediate risk features or in individuals who fail to achieve a remission with standard dose chemotherapy.

Koreth and colleagues (2009) conducted a systematic review and meta-analysis of allogeneic stem cell transplantation for individuals with AML in CR1. Twenty-four prospective trials with 6007 assigned participants were analyzed for relapse-free survival (RFS) and OS stratified by good-, intermediate-, and poor-risk AML. Compared to non-allogeneic treatment modalities (e.g., consolidation chemotherapy, autologous stem cell transplantation [SCT] or both) for AML in CR1, good-risk AML had a combined hazard ratio (HR) of 1.06 (95% confidence interval [CI], 0.80-1.42) indicating a lack of RFS benefit (p=0.68). Intermediate-risk AML had a combined HR of 0.76 (95% CI, 0.68-0.85) with a significant RFS benefit (p<0.01) with allogeneic SCT. Similarly, poor-risk AML had a combined HR of 0.69 (95% CI, 0.57-0.84) with a significant RFS with allogeneic SCT. The authors concluded “SCT does not provide significant benefit for good-risk AML in CR1 and that allogeneic SCT offers significant RFS and overall survival benefits for intermediate- and poor-risk AML in CR1” (Koreth, 2009).

The Center for International Blood and Marrow Transplantation Research (CIBMTR, Keating, 2012) analyzed data for autologous HSCT compared to HLA-identical sibling allogeneic HSCT for treatment of AML in CR1. Although autologous HSCTs have been used when there have been no suitable allogeneic donors, higher rates of relapsed disease have resulted after autologous HSCT. Based on the CIBMTR data, the authors concluded “Treatment failure (death or relapse) after autologous peripheral blood was significantly more likely [relative risk 1.32 (1.06-1.64); p=0.011].” Later studies have supported these findings (Chevallier, 2015; Ma, 2015). NCCN does not recommend autologous HCT as a treatment of AML.

The National Marrow Donor Program notes “Allogeneic transplant following myeloablative conditioning is currently considered the most effective anti-leukemic treatment option for adults with acute myelogenous leukemia (AML) in remission.”

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Bejanyan and colleagues (2015) reported outcomes data from the Center for International Blood and Marrow Transplant Research (CIBMTR) database of 1788 individuals with AML who relapsed after an alloHSCT and compared factors and clinical outcomes associated with survival. There was a significant association of lower mortality with longer time from allogeneic HSCT to relapse (relapse rate [RR], 0.55 for 6 months to 2 years; RR, 0.39 for 2-3 years; and RR, 0.28 for  $\geq 3$  years). The authors concluded individuals with relapsed disease  $\geq 6$  months after the initial HSCT had better survival and could benefit from a second cell-based therapy (allogeneic HSCT  $\pm$  donor lymphocyte infusion). Based on the data from published peer reviewed literature, specialty consensus opinion recommends the use of a second allogeneic HSCT for relapsed AML after the initial allogeneic HSCT.

Wang and colleagues (2010) reported data from a meta-analysis of randomized trials of autologous HSCT treatment of AML in CR1. The authors noted the use of autologous HSCT in the management of AML remains “contentious.” Data from 13 studies involving 12 randomized controlled trials, which included both pediatric and adult populations, were included in the meta-analysis. For adults, autologous HSCT had higher transplant-related mortality (TRM) and lower relapse rate compared to non-transplant therapy. Participants randomized to autologous HSCT had a significantly higher risk of death in CR1 compared to those assigned to receive chemotherapy or no further therapy (RR, 1.90, 95% CI, 1.34-2.70). There was a significant disease-free survival (DFS) with autologous HSCT compared to chemotherapy alone (HR, 0.89; 95% CI, 0.80-0.98). When the studies were pooled by age, DFS was not significantly different in children, and the significant difference remained for adults who had HSCT. However, the DFS did not translate to a difference in OS (HR, 1.05; 95% CI, 0.91-1.21). The authors concluded that “Autologous SCT should not be considered as the first-line post-remission therapy for AML in patients in CR1.”

Approximately 50 to 70% of individuals with AML are expected to relapse after attaining a first complete remission (Rai, 2001). Conventional chemotherapy is generally not curative once relapse occurs, even if a second complete remission can be achieved. High dose chemotherapy with allogeneic HSCT is associated with a prolonged DFS in 30%-40% of individuals in first relapse or second complete remission. Due to the mortality associated with remission induction, allogeneic SCT may be considered as the initial treatment of relapsed disease. In individuals without an allogeneic donor, or those who are not candidates for allogeneic stem cell support due to age or other factors, autologous HSCT may be considered after a second complete remission. However, there may be contamination of the autologous stem cell populations by malignant cells.

Based on the data from published peer reviewed literature, specialty consensus opinion recommends the use of allogeneic HSCT as an effective treatment for children and adults with AML.

## **ALL**

ALL is a heterogenous hematologic disorder characterized by the presence of too many lymphoblasts or lymphocytes in the bone marrow and the peripheral blood. ALL is an aggressive type of leukemia and can spread to the central nervous system and other organs. ALL is the most common type of cancer in children but can occur at any age. There is no clear age cut-off that distinguishes adult from childhood ALL; disease is classified as untreated, in remission, or recurrent. Published data generally group therapies and outcomes according to risk stratification (NCCN, V2.2024; NCI, 2024). The NCI stratifies the pediatric population into the following: infants (< 1 year); age 1 to < 10 years; adolescents and young adults ( $\geq 10$  years). NCCN stratifies individuals by risk factors and ages 15-39 years as adolescent and young adult (AYA), and adult as  $\geq 40$  years of age.

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**Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome**

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In 2012, the American Society for Transplantation and Cellular Therapy (ASTCT), (previously the American Society for Blood and Marrow Transplantation [ASBMT]) Position Statement on the role of stem cell transplantation in the treatment of pediatric ALL was updated with an evidence-based review (Oliansky, 2012a). The recommendations were based on consensus of an expert panel after a systematic review of the literature published since the 2005 review. The updated review of evidence published in the literature included 13 studies comparing chemotherapy to HSCT for children with ALL in CR1, greater than or equal to second complete remission (CR2), or with relapsed disease. Based on new data, autologous stem cell transplant (SCT) “is not a recommended treatment, nor is it standard practice. There are no data to support a benefit for autologous SCT in children.”

The ASBMT Position Statement for treatment of adult ALL was also updated in 2012 (Oliansky, 2012b). The recommendation states, “New data strengthen the original treatment recommendation favoring allogeneic over autologous SCT.” Additionally, the new data in the statement confirm, “Myeloablative allogeneic SCT is an appropriate treatment for adult ALL in CR1 for all disease risk groups.”

There is a strong correlation between the presence of minimal residual disease (MRD) and the risk of relapse in children and adults. The NCCN Clinical Practice Guideline (CPG) V2.2023 for ALL notes that individuals classified as having CR based on morphologic assessment methods can have up to  $10^{10}$  leukemic cells. Bruggemann and colleagues (2006) evaluated the predictive value of MRD in 196 standard risk individuals with ALL. Individuals were monitored for MRD at nine points during the first year of treatment. On day 24, the relative risk of relapse for individuals with MRD levels  $10^{-4}$  (0.01%) of bone marrow mononuclear cells or higher was 2.4 (95% CI, 1.3-4.2) when compared to individuals with MRD levels below  $10^{-4}$  %. The prognostic value of MRD as well as the use of MRD as a decisional tool has since been validated in multiple studies (Bassan, 2009; Coustan-Smith, 2000; Patel, 2010; Ravandi, 2016; Vidriales, 2003; Vora, 2013).

A Cochrane Review (Pidala, 2011) evaluated results from 14 clinical trials and compared allogeneic HSCT, autologous HSCT and chemotherapy as treatment for adults with ALL in CR1. The authors concluded from the systematic review and meta-analysis that matched related sibling donor allogeneic HSCT is:

The optimal post-remission therapy in ALL patients aged 15 years or over. This therapy offers superior overall survival (HR 0.86; 95% CI, 0.77 to 0.97;  $p=0.01$ ) and DFS (HR 0.82; 95% CI, 0.72 to 0.94;  $p=0.004$ ), and significantly reduces the risk of disease relapse (RR 0.53; 95% CI, 0.37 to 0.76;  $p=0.0004$ ), but does impose an increased risk of non-relapse mortality (RR 2.8; 95% CI, 1.66 to 4.73;  $p=0.001$ ).

Additionally, specialty consensus opinion recommends the use of allogeneic HSCT as a treatment for children and adults with ALL.

The NCCN CPG (V2.2024) recommends participation in clinical trials, chemotherapy or an allogeneic HCT for adults with relapsed/refractory disease after an initial CR for individuals with Ph-negative ALL. For individuals with relapsed disease following an allogeneic HCT, the NCCN guidelines note that a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.

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**Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome**

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Approximately 30% of all adult cases have chromosomal abnormalities such as Philadelphia chromosome (Ph1)-positive t(9;22) or aneuploidy, which may correlate with poor prognosis. Ph1 t(9;22) occurs in approximately 3% of children with ALL. Additional cytogenetic and chromosomal abnormalities listed as poor risk indicators include deletion of chromosome 7, trisomy 8, B-cell lineage ALL with an L3 phenotype (surface immunoglobulin positive), and B-cell lineage ALL characterized by t(4;11) (NCI, 2023). There are ongoing studies that incorporate targeted therapies (e.g., imatinib) to determine the optimal timing with HSCT, to improve outcomes and reduce relapse rates for individuals with high-risk indicators.

Schultz and colleagues (2007) reported results of a retrospective analysis of cytogenetic data in 6238 individuals. There was concordance supporting hypodiploidy, or less than 44 chromosomes and 11q23 (MLL) translocation as high-risk indicators. Individuals should be selected for treatment with high-dose chemotherapy plus stem cell support using risk-directed strategies. Two randomized controlled trials and one large registry-based retrospective review were published on high-dose chemotherapy with stem cell support to treat ALL in adults (Bhatia, 1997; Champlin, 2000). These studies did not compare outcome after high-dose chemotherapy to outcome after conventional-dose chemotherapy, but rather compared (a) outcome according to stem cell source (bone marrow or peripheral blood); (b) outcome using primed or unprimed peripheral blood stem cells; or (c) the benefits of adding interleukin-2 as post-transplant therapy. The results of these studies and several dozen uncontrolled clinical series confirm the existing position on the use of high-dose chemotherapy plus allogeneic stem cell support to treat adult ALL in first or subsequent remission or in relapse.

Mixed phenotype acute leukemia (MPAL), previously known as biphenotypic acute leukemia, is a subtype of acute leukemias which contain two distinct lymphoblastic populations, one of which meets the criteria for AML. MPAL accounts for approximately 2-5% of the cases of acute leukemia (Khan, 2018). This population has not been well-studied, individuals have frequently been excluded from clinical studies, but treatment generally follows ALL regimens. Outcomes in this group are generally worse than both ALL and AML (Khan, 2018).

**CML**

Since response rates with tyrosine kinase inhibitors (TKIs) have been favorable as first or second line therapies for chronic phase CML, the NCCN notes that the role of allogeneic hematopoietic stem cell transplant (HCT) as first-line therapy has changed. HCT is no longer recommended as a first-line treatment for chronic phase CML (NCCN, V1.2025). Allogeneic HCT is recommended for individuals presenting with blast phase (BP) CML and those who have progressed to accelerated phase (AP) or BP CML while on TKIs. Allogeneic HCT is recommended for individuals with T315I and other BCR-ABL1 mutations and are unresponsive or intolerant to all TKIs. Additionally, individuals with progression of CML to accelerated or blast phase on tyrosine kinase inhibitor therapy should be considered for allogeneic HCT. Survival rates are better for individuals transplanted in chronic phase compared to those with advanced disease. Five-year survival for individuals with chronic, accelerated and blast crisis phases treated with matched-related transplants are approximately 75%, 40% and 10% respectively.

**CLL/SLL**

Magni and colleagues (2014) reported results from a phase III multi-center randomized controlled trial (RCT) that investigated the use of rituximab, fludarabine and cyclophosphamide (R-FC) compared to high-dose sequential (R-HDS) chemotherapy followed by an autologous SCT (ASCT) as frontline treatment for individuals with CLL. A total of 96 individuals were randomized and 48 participants were assigned to each group. There was no statistically

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**Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome**

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significant improvement in PFS and OS between the groups after 5 years of follow-up. The PFS for the R-HDS group was 60.4% and 65.1% ( $p=0.66$ ) for the R-FC group. The OS was similar for the R-HDS group (88.0%) compared to the R-FC group (88.1%). The authors concluded that the use of upfront ASCT should not be recommended compared to optimal chemoimmunotherapy regimens. There is a lack of additional randomized trials that report the outcomes of high-dose chemotherapy followed by autologous stem cell transplant compared to conventional therapy.

In a multi-center study reported by Sorrow and colleagues (2005), 64 individuals diagnosed with advanced CLL were treated with nonmyeloablative chemotherapy and allogeneic stem cell transplant from related ( $n=44$ ) or unrelated ( $n=20$ ) donors. Out of 64 individuals, 61 participants had sustained engraftment, whereas 3 participants rejected their grafts. Three individuals who underwent transplantation in complete remission (CR) remained in CR. The overall response rate among 61 individuals with measurable disease was 67% (50% CR), whereas 5% had stable disease. All individuals with morphologic CR who were tested by polymerase chain reaction ( $n=11$ ) achieved negative molecular results, and one of these individuals subsequently experienced disease relapse. The 2-year incidence of relapse/progression was 26%, whereas the 2-year relapse and non-relapse mortalities were 18% and 22%, respectively. Two-year rates of overall and DFS were 60% and 52%, respectively. Unrelated transplants resulted in higher CR and lower relapse rates than related transplants, suggesting more effective graft vs leukemia activity. Therefore, allogeneic stem cell transplant appears to prolong median survival for individuals with advanced CLL.

**MDS/MPN**

The term chronic myeloproliferative disease or disorder was changed to “myeloproliferative neoplasm” to more accurately reflect the neoplastic nature of the disease entities (Vardiman 2009). WHO’s 2016 classification of myeloproliferative neoplasms includes chronic myelomonocytic leukemia (CMML), atypical CML, juvenile myelomonocytic leukemia (JMML), unclassified MDS/MPN and myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) (Arber, 2016). Conditions that contain both ineffective maturation with dysplastic features (MDS), or both ineffective and defective maturation, are categorized as (myelodysplastic/myeloproliferative neoplasms (MDS/MPN) (Vardiman, 2010).

The IPSS score has been used as a prognostic tool to predict progression and plan therapy in adults with primary untreated MDS. This tool was developed in 1997 and has shown strong prognostic value in adult population. Since then, efforts have been made to refine the IPSS by incorporating additional prognostic features into the prognostic model. The Revised International Prognostic Scoring System (IPSS-R) expanded the major prognostic categories from 4 to 5 (Greenberg, 2012). Although other scoring systems are valuable, the IPSS-R is preferred given its more accurate risk stratification (NCCN, V3.2024). Like the IPSS, the IPSS-R has limited value in the pediatric population and is intended to be used only in adults (Greenberg, 2012). HCT is considered a potentially curative therapy in the majority of children with MDS or JMML and is recommended to be performed prior to progression or the appearance of complications (Hasle, 2014).

The treatment options for CMML are similar to MDS. There has been only modest success with standard chemotherapy regimens. Intensive chemotherapy alone is of little benefit. Allogeneic stem cell transplantation is the only potential curative therapy.

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**MDS**

According to NCCN (V3.2024), allogeneic hematopoietic cell transplant (HCT) is indicated at diagnosis for individuals with an IPSS INT-2 score and for high-risk individuals less than or equal to 60 years of age. Individuals with low or INT-1 classifications without severe cytopenias may benefit from delaying transplantation for several years or until prior to disease progression.

MDS caused by prior cancer therapy (chemotherapy and/or radiation therapy) or develops in individuals with bone marrow disease is categorized as secondary MDS or treatment related MDS (American Cancer Society, 2022). Oran and colleagues (2013) noted individuals with intermediate-2 and high-risk disease and those with therapy-related MDS have a poor prognosis with conventional chemotherapy. Allogeneic HCT is the treatment with the curative potential by replacing the abnormal blood cells in the bone marrow with healthy donor stem cells. The use of a second allogeneic HCT is also being considered for individuals who experience prolonged remission following the initial HCT. Comparative clinical trials are needed to further evaluate the safety and efficacy of this therapy compared to standard therapies (NCCN, V3.2024).

Allogeneic HCTs are more effective than autologous transplants in preventing relapses because the donor cells recognize the cancer as foreign and kill the cancer cells immunologically. This response is called the graft vs leukemia reaction and is related to graft vs host disease (GVHD). The graft vs leukemia reaction is stronger in acute GVHD than in chronic GVHD. The lack of GVHD is associated with an increased risk of relapse.

The incidence of MDS and myelodysplasia in children is very low, occurring in 1-4 cases/million/year (NCCN, V3.2024). Due to the rarity and heterogeneity of MDS in the pediatric population, there is a lack of clinical trials. For the pediatric population, the goal of treatment is curative rather than palliative. HCT is considered the only curative treatment option in childhood MDS (NCCN, V3.2024). Germing and colleagues (2008) noted that, “as most children are grafted, the IPSS for MDS in adults is of limited value in children”.

**Poor Graft Function**

Poor graft function or graft failure is a major cause of morbidity and mortality after HSCT. Poor graft function is defined as slow or incomplete recovery of blood cell counts following a stem cell transplant or decreasing blood counts after initially successful hematopoietic engraftment following a SCT. There are various options for the management of poor graft function. Stem cell “boost” is a non-standardized term that is used to describe an infusion of additional hematopoietic stem cells to an individual who has undergone a recent hematopoietic stem cell transplantation and has poor graft function (Larocca, 2006). Infusion of additional hematopoietic stem cells with or without immunosuppression is done to mitigate either graft failure or rejection. This process may include the collection of additional hematopoietic stem cells from a donor and infusion into the transplant recipient. Note that a “boost” is distinct from a repeat transplant and that there may be separate medical necessity criteria for a repeat transplant.

**HCT and Human Immunodeficiency Virus (HIV) status**

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The number of individuals living with HIV who require a stem cell transplant is increasing as this population grows in number and ages. Older individuals with HIV have an increased risk of developing malignancies which require stem cell transplantation (Ambinder, 2020; Murray, 2021). With the development of more effective treatments, HIV infection is not a contraindication to stem cell transplants and does not adversely affect outcomes. There are some additional risks associated with long-term management, such as a potential for viral rebound if antiretroviral therapy is interrupted. Allogeneic stem cell transplants may also offer the opportunity for HIV cure in limited circumstances. (Ambinder, 2020; Capoferri, 2022; Murray, 2021).

### Background/Overview

The introduction of targeted therapies, such as CAR T-cell therapy and immunotherapy have been important additions into many cancer treatment plans. These treatments have many times become first or second line recommended lines of therapy. HSCT remains an important treatment for many malignant and nonmalignant hematologic diseases. Its applicability continues to expand as techniques are refined and new indications are identified. The number of individuals who could benefit from HSCT has increased due to advancements such as reduced intensity conditioning regimens that have made HSCT safer (Majhail, 2015). However, the potential for transplant-associated morbidity and mortality remains significant. Most transplant centers use forums, boards or conferences where the treatment options of individual HSCT candidates are discussed (Majhail, 2015). Okamoto (2017) notes:

The medical decision-making process for a transplant procedure is complex which requires assessing several factors besides the underlying indication for transplantation. Those include patient/disease factors, and transplant factors such as planned conditioning/graft vs host disease (GVHD) prophylaxis and stem cell source. Patient factors include their overall health and comorbidities, prior therapies, and how patients responded to those therapies, age, and disease/disease risk.

There are a number of clinical assessment and prognostic tools which evaluate individuals diagnosed with cancers based upon multiple factors. The earlier, simpler tools, such as the Charlson Comorbidity Index (CCI) were useful in predicting outcomes, but lacked the sensitivity of subsequent tools such as the HCT-specific comorbidity index (HCT-CI). The HCT-CI score has been validated in multiple HSCT settings to independently predict non-relapse mortality (NRM) rates by weighting 17 relevant comorbidities. The HCT-CI was further enhanced by the incorporation of some laboratory biomarkers into an augmented version. While these tools provide valuable prognostic information, the decision to transplant is unique to each individual and needs to include a specific risk-benefit analysis in partnership with the individual's physicians and other caregivers.

### *Specific Conditions*

AML, sometimes called acute non-lymphocytic leukemia (ANLL), refers to a malignancy arising from a myeloid precursor in the bone marrow. It is the most common form of leukemia among older persons. AML incidence rates increase dramatically among people who are over the age of 40. It is most prevalent in the sixth, seventh and eighth decade of life.

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**Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome**

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Acute promyelocytic leukemia (APL), an aggressive AML subtype, comprises approximately 10% of all AML cases. APL is distinguished by a t(15;17) chromosomal translocation. APL may arise de novo or in relation to chemotherapy, but both variations are treated similarly. Current APL induction therapies are associated with favorable outcomes. The objective of consolidation therapy is to achieve a durable molecular remission.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare subtype of acute leukemia which is derived from the precursors of plasmacytoid dendritic cells. In 2008, the World Health Organization (WHO) classified BPDCN as an “acute myeloid leukemia (AML) and related precursor neoplasm”. In 2016, BPDCN was classified into a separate category under myeloid neoplasms. BPDCN is generally aggressive and the prognosis is poor; the median overall survival is approximately 1 year. There are no standard therapies for BPDCN. Affected individuals are typically treated with chemotherapy regimens used for AML, ALL or lymphoma. While BPDCN often responds to chemotherapy, the disease often relapses (Aoki, 2015; Kharfan-Dabaja, 2017; Pagano, 2013; Roos-Weil, 2013).

ALL is a heterogeneous group of malignancies arising from lymphocytic precursors. The malignant clone may be derived from a T or B cell as shown by the expression of different surface antigens. The different subtypes of ALL are also heterogeneous with respect to their response to chemotherapy and to their age distribution (i.e., different subtypes typically occur in children and adults). Approximately 80% of ALL cells are classified as early B-cells, 10%-15% are T-cells and approximately < 5% are B-cells with surface immunoglobulins (NCI, 2023). ALL has a bimodal age distribution with an initial peak at 2-3 years, with the incidence again increasing after the age of 50. By definition, ALL primarily affects the bone marrow, but in advanced cases it can involve lymph nodes, liver, spleen and the central nervous system (CNS). Although the cause of leukemia is not known in most individuals, epidemiologic evidence suggests that genetics and environmental factors may play a role in its development.

CML is a malignancy arising from a primitive hematopoietic stem cell. It is characterized by the presence of a chromosomal abnormality called the "Philadelphia" chromosome. This abnormality results from reciprocal translocation of genetic material between chromosomes 9 and 14. This results in the expression of an abnormal protein that acts as an enzyme that stimulates cell proliferation. This enzyme is found only in the malignant cells. CML annually accounts for approximately 15% of all newly diagnosed adult leukemia cases. The annual mortality of CML has decreased from a high of 10-20% affected persons to 1-2% with the introduction of TKIs in 2000 (Jabbour, 2022).

TKI therapy represents an effective, targeted approach to interfere with the cellular proliferation of malignant cells. The TKIs, including imatinib, dasatinib, bosutinib and nilotinib, are approved by the U.S. Food and Drug Administration (FDA) for the treatment of CML. Second and third generation therapies including dasatinib, bosutinib and nilotinib, are considered more potent and achieve higher rates of durable deep/complete molecular responses than the original TKI, imatinib (Firwana, 2015, Jabbour, 2022). Allogeneic stem cell transplantation is the only therapy that can be considered curative; however, it is associated with a risk of increased morbidity and mortality (Jabbour, 2022; NCCN, V1.2025)

CLL and SLL are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes that have a mature, generally well-differentiated morphology. In CLL, these cells accumulate in the blood, marrow, lymph nodes, and spleen. In SLL, they are generally confined to the lymph nodes. CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other. Both tend to occur in older

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## Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome

individuals and present as asymptomatic enlargement of the lymph nodes. Both tend to be indolent in nature but can undergo transformation to a more aggressive form of disease. Treatment regimens used for CLL are generally the same as those used for SLL and outcomes of treatment are comparable for the two diseases. Both low and intermediate risk CLL and SLL demonstrate relatively good prognoses with median survivals of 6 to 10 years, while the median survival of high risk CLL or SLL may be only 2 years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy and nearly all individuals ultimately die of their disease.

MDS/MPN are clonal myeloid disorders with features that are both dysplastic and proliferative but are not strictly classified as either MDS or chronic myeloproliferative disorders (CMPD). The three major myeloid disorders in this category include: chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), and atypical chronic myeloid leukemia (aCML) (NCI, 2023). In addition, refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) has been recognized as a separate entity within this category. WHO reclassified these previous MDS disorders based on the French-American-British (FAB) classification system, into a separate category of MDS/MPN. Various chemotherapy regimens have been used with limited success. Treatment of CMML remains challenging with no proven strategy prolonging survival. NCCN's CPG for MDS recommends treatment of CMML in a manner similar to treatment of MDS, including high dose chemotherapy followed by allogeneic hematopoietic stem cell transplantation.

MDS refers to a heterogeneous group of clonal hematopoietic disorders characterized by impaired maturation of hematopoietic cells and a tendency to transform into AML. MDS can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental exposure. Chromosomal abnormalities are seen in 40%-60% of individuals, frequently involving deletions of chromosome 5 or 7, or an extra chromosome (e.g., trisomy 8).

The myeloproliferative neoplasms are characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML.

High-dose chemotherapy (HDC) involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. This process, called the conditioning regimen, is used to kill as many tumor cells as possible and to prepare the bone marrow for transplantation. Many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage can result in relatively large increases in tumor cell death. Although bone marrow ablation is an intended effect of HDC, it can result in severe side effects such as opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is an intended effect of HDC. Following this ablation, transfused hematopoietic stem cells reconstitute the marrow and begin their replication, formation into mature blood cells, and reconstitution of the immune system. The potential sources of stem cells include:

1. Autologous - Stem cells harvested from the individual's own bone marrow or peripheral blood
2. Allogeneic - Stem cells harvested from a histocompatible donor (**Note:** this document does not require a specific level of histocompatibility be present as part of the medical necessity evaluation)

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**Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome**

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Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy or hematopoietic growth factors, or both.

In addition, blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically “naïve” and are associated with a lower incidence of rejection or graft vs host disease.

Immunologic compatibility between donor and recipient is a critical factor for achieving a good outcome of allogeneic bone marrow transplantation. Compatibility is established by typing of human lymphocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on the long arm of chromosome 6.

The most appropriate stem cell source for a particular individual depends upon their disease, treatment history, and the availability of a compatible donor. The selection of the most appropriate source of stem cells for each individual must balance the risks of graft failure, or re-infusion of malignant cells in autologous procedures and the risks of graft rejection or GVHD in allogeneic procedures.

While some HDC protocols can be administered on an outpatient basis, an inpatient stay is often required. Individuals receiving whole body radiotherapy and those receiving an allogeneic transplant might require prolonged hospitalization.

While the intensity of the regimens used for conditioning in conventional HDC varies, collectively they have been termed “myeloablative.” Several less intense conditioning regimens have been developed recently and rely more on immunosuppression than cytotoxic effects. This may promote engraftment of donor cells. These regimens, collectively termed “non-myeloablative” also vary in intensity with substantial overlap between the ranges for “myeloablative” and “non-myeloablative” regimens. Studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. This results in stable mixed donor-host hematopoietic chimerism. Once chimerism has developed, a further infusion of donor leukocytes may be given to eradicate malignant cells by inducing a graft vs. tumor effect. Non-myeloablative allogeneic transplants, also referred to as “mini-transplant” or “transplant lite”, are thought to be potentially as effective as conventional HDC followed by an allogeneic stem cell transplantation (AlloBMT), but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen. Consequently, for individuals with malignancies who are eligible for conventional HDC/AlloBMT, conditioning with milder, non-myeloablative regimens (NM-AlloBMT) represents a technical modification of an established procedure.

Tandem high-dose or non-myeloablative chemotherapy with autologous or allogeneic stem cell support is the planned administration of more than one cycle of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The

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hypothesis is that eradication of residual tumor cells can be achieved using multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

### Definitions

**Ablative:** Very high dose of a treatment that is calculated to kill a tumor.

**Blast Crisis:** Phase in CML in which more than 30% of cells in the blood or bone marrow are immature (blast cells). Symptoms include fatigue, fever and an enlarged spleen.

**Bone marrow:** A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

**Chemosensitive:** Showing tumor response to the most recent chemotherapy regimen.

**Chemotherapy:** Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

**Chimerism:** Cell populations derived from different individuals; may be mixed or complete.

**Complete response/remission (CR):** The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured; also called a complete response.

**Cytotoxic:** Destructive to cells.

**Doubling time:** The amount of time it takes for one cell to divide or for a group of cells (such as a tumor) to double in size. The doubling time may vary for different kinds of cancer cells or tumors.

**Failure to engraft:** When the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

**Graft vs host disease (GVHD):** A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

**Hematopoietic stem cells:** Cells that give rise to distinct daughter cells, one cell that replicates the stem cell and one cell that will further proliferate and differentiate into a mature blood cell.

**High-dose or myeloablative chemotherapy (HDC):** The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

**HLA (human leukocyte antigen):** A group of protein molecules located on bone marrow cells that can provoke an immune response.

**International Prognostic Scoring System (IPSS<sup>g,h</sup>):**

Survival and AML evolution					
	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%) <sup>i</sup>	< 5	5-10	---	11-20	21-30

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Karotype <sup>j</sup>	Good	Intermediate	Poor		
Cytopenia <sup>k</sup>	0/1	2/3			

<sup>g</sup> Greenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.

<sup>h</sup> Greenberg P, Cox C, LeBeau M, et al. Erratum. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1998;91:1100.

<sup>i</sup> Patients with 20-30 % blasts may be considered as MDS or AML.

<sup>j</sup> Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. [This excludes karyotypes t(8;21), inv16, and t(15;17), which are considered to be AML not MDS.]

<sup>k</sup> Cytopenias: neutrophil count <1,800/mcL, platelets < 100,000/mcL, Hb < 10g/dL.

### International Prognostic Scoring System-Revised (IPSS-R<sup>1</sup>)

	Score value						
Prognostic variable	0	0.5	1.0	1.5	2	3	4
Cytogenetics	Very good	n/a	Good	n/a	Intermediate	Poor	Very poor
Bone marrow blast (%)	≤ 2	n/a	> 2 to < 5	n/a	5 to	>10	n/a
Hemoglobin	≥ 10		8 to < 10	< 8	n/a	n/a	n/a
Platelets	≥ 100	50 to < 100	< 50	n/a	n/a	n/a	n/a
ANC	≥ 0.8	< 0.8	n/a	n/a	n/a	n/a	n/a

ANC – Absolute neutrophil count

n/a – not applicable

Risk category	Risk Score
Very low	≤ 1.5
Low	> 1.5 to ≤ 3
Intermediate	> 3.0 to ≤ 4.5
High	> 4.5 to ≤ 6.0
Very high	> 6.0

<sup>1</sup>Greenberg P, Heinz T, Schanz J, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood. 2012;120: 2454-2465.

**Minimal Residual Disease (MRD):** The presence of leukemic cells at a level not detectable using conventional morphologic methods.

**Myelodysplastic syndrome (MDS):** Conditions that occur when the blood-forming cells in the bone marrow are damaged.

**Primary MDS:** Initial MDS diagnosis, usually when a cause is unknown; also known as primary MDS.

**Secondary MDS:** When a cause for the disease is known. Common causes include earlier treatment for a cancer; also known as treatment related MDS.

**Non-myeloablative chemotherapy:** Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

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**Partial response:** A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment; also called partial remission.

**Primary graft failure:** When the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

**Primary refractory disease:** Cancer that does not respond at the beginning of treatment; also called resistant disease.

**Relapse:** After a period of improvement, the return of signs and symptoms of cancer.

**Tandem:** Planned administration of more than one cycle of high-dose or non-myeloablative chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells; also known as double transplant.

### Coding

*The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

### When services may be Medically Necessary when criteria are met for allogeneic transplants:

#### CPT

38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; specified as allogeneic]
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38243	Hematopoietic progenitor cell (HPC); HPC boost

#### HCPCS

S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition [specified as allogeneic]

#### ICD-10 Procedure

*Allogeneic transplantation*

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## Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome

30233G2-30243G4	Transfusion of allogeneic bone marrow, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233G2, 30233G3, 30233G4, 30243G2, 30243G3, 30243G4]
30233U2-30243U4	Transfusion of allogeneic T-cell depleted hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233U2, 30233U3, 30233U4, 30243U2, 30243U3, 30243U4]
30233X2-30243X4	Transfusion of allogeneic cord blood stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233X2, 30233X3, 30233X4, 30243X2, 30243X3, 30243X4]
30233Y2-30243Y4	Transfusion of allogeneic hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233Y2, 30233Y3, 30233Y4, 30243Y2, 30243Y3, 30243Y4]
	<i>Pheresis [when specified as allogeneic]</i>
6A550ZV	Pheresis of hematopoietic stem cells, single [when specified as allogeneic]
6A551ZV	Pheresis of hematopoietic stem cells, multiple [when specified as allogeneic]

### ICD-10 Diagnosis

C83.00-C83.0A	Small cell B-cell lymphoma
C83.50-C83.5A	Lymphoblastic (diffuse) lymphoma
C91.00-C91.92	Lymphoid leukemia
C92.00-C92.92	Myeloid leukemia
C94.40-C94.42	Acute panmyelosis with myelofibrosis (acute myelofibrosis)
D46.0-D46.9	Myelodysplastic syndromes
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D75.81	Myelofibrosis

### When services are Investigational and Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

### When services are Investigational and Not Medically Necessary for autologous transplants:

When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

### CPT

38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; specified as autologous]
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

### HCCPS

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## Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome

S2150 Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition [specified as autologous]

### ICD-10 Procedure

*Autologous transplantation*

30233G0-30243G0 Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]

30233Y0-30243Y0 Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]

*Pheresis [when specified as autologous]*

6A550ZV Pheresis of hematopoietic stem cells, single [when specified as autologous]

6A551ZV Pheresis of hematopoietic stem cells, multiple [when specified as autologous]

### ICD-10 Diagnosis

C83.00-C83.0A Small cell B-cell lymphoma

C83.50-C83.5A Lymphoblastic (diffuse) lymphoma

C91.00-C91.92 Lymphoid leukemia

C92.00-C92.92 Myeloid leukemia

C94.40-C94.42 Acute panmyelosis with myelofibrosis

D45 Polycythemia vera

D46.0-D46.9 Myelodysplastic syndrome

D47.1 Chronic myeloproliferative disease

D47.4 Osteomyelofibrosis

D75.81 Myelofibrosis

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  - Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.1.2025. Revised October 1, 2024.
  - Chronic Myeloid Leukemia V.1.2025. Revised August 8, 2024.

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## Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome

- Hematopoietic Cell Transplantation (HCT) V.2.2024. Revised August 30, 2024.
  - Myelodysplastic Syndromes V.3.2024. Revised July 25, 2024.
  - Myeloproliferative Neoplasms V.2.2024. Revised August 8, 2024.
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### Websites for Additional Information

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3. National Marrow Donor Program. Consultation guidelines & outcome. Available at: [Consultation guidelines & outcomes / NMDP](#). Accessed on October 22, 2024.

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Peripheral Blood Stem Cell  
Stem Cell Support (SCS)  
Stem Cell Transplant (SCT)

**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

### Document History

Status	Date	Action
Revised	11/14/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised formatting in Position Statement section. Revised Description, Rationale, Background and References sections.
	10/01/2024	Updated Coding section with 10/01/2024 ICD-10-CM changes; added C83.0A and C83.5A to end of ranges.
Reviewed	11/09/2023	MPTAC review. Updated Rationale, Background and References sections.
Revised	11/10/2022	MPTAC review. Revised the AML criteria remove “favorable classification” as the required criteria and replace the required criteria with the specific conditions considered favorable classification without a change in intent. Updated Rationale, Background and References sections. Updated coding section.
Revised	11/11/2021	MPTAC review. Revised the MDS position statement to add IPSS-R criteria. Updated Rationale, Background and References sections.
	10/01/2021	Updated Coding section with 10/01/2021 ICD-10-PCS changes; removed open approach codes deleted 09/30/2021.
Reviewed	11/05/2020	MPTAC review. Updated Rationale, Background and References sections. Updated Coding section.
Reviewed	11/07/2019	MPTAC review. Updated Rationale, Background and References sections.
	10/01/2019	Updated Coding section with 10/01/2019 ICD-10-PCS changes; added 30230U2-30243U4; removed 30250G0-30263G1, 30250X1-30263Y1 deleted 09/30/2019.
Revised	11/08/2018	MPTAC review.
Revised	10/31/2018	Hematology/Oncology Subcommittee review. Revised ALL medically necessary criteria to include <i>minimal residual disease positivity following induction</i> to the list of high risk indications. Revised CLL/SLL medically necessary statement to remove criteria regarding responsiveness to salvage therapy and Rai high risk factors and to add medically necessary criteria regarding those refractory to small molecule inhibitor therapy. Updated Rationale, Background and References sections.
Revised	11/02/2017	MPTAC review.
Revised	11/01/2017	Hematology/Oncology Subcommittee review. Removed Individual Selection criteria. Revised AML and CML to myeloid from myelogenous. Revised <i>category Chronic Myelomonocytic Leukemia (CMML), Myelodysplastic Syndrome (MDS), Juvenile Myelomonocytic Leukemia (JMML) and other Myeloproliferative Neoplasms (MPN) to Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN)</i>

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## Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome

		<i>or Myelodysplastic Syndrome (MDS)</i> . The document header wording updated from “Current Effective Date” to “Publish Date”. Updated Description, Rationale, Background and References sections.
Revised	05/04/2017	MPTAC review.
Revised	05/03/2017	Hematology/Oncology Subcommittee review. Revised Individual Selection Criteria regarding hepatic insufficiency to require either a bilirubin or INR result. Added a note regarding the pediatric population to the <i>de novo or primary</i> myelodysplastic syndrome medically necessary criteria. Updated Rationale, Background, References and Websites sections. Updated formatting in Position Statement section.
	10/01/2016	Updated Coding section with 10/01/2016 ICD-10-PCS procedure code changes.
Reviewed	05/05/2016	MPTAC review.
Reviewed	05/04/2016	Hematology/Oncology Subcommittee review. Updated Rationale, Background, Definitions, References and Websites sections. Removed ICD-9 codes from Coding section.
Revised	05/07/2015	MPTAC review.
Revised	05/06/2015	Hematology/Oncology Subcommittee review. Added medically necessary criterion for a second allogeneic HSCT for relapsed AML. Updated Rationale, References and Websites sections.
Reviewed	05/15/2014	MPTAC review.
Reviewed	05/14/2014	Hematology/Oncology Subcommittee review. Reformatted medically necessary criteria for ALL. Clarified medically necessary criteria for <i>de novo</i> or primary myelodysplastic syndrome (MDS). . Added allogeneic (ablative and non-myeloablative) stem cell transplant as medically necessary for individuals who have secondary MDS. Updated Rationale, References and Websites sections.
Revised	05/09/2013	MPTAC review.
Revised	05/08/2013	Hematology/Oncology Subcommittee review. Removed medically necessary indications for autologous HSCT for AML and ALL. Added medically necessary indications for CML – accelerated and blast phases. Added investigational and not medically necessary criteria for autologous HSCT for AML and ALL. Updated Rationale, Coding, References and Websites sections.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes.
Revised	05/10/2012	MPTAC review.
Revised	05/09/2012	Hematology/Oncology Subcommittee review. Clarified medically necessary and investigational and not medically necessary harvest criterion. Clarified hepatic insufficiency Individual Selection Criterion. Updated Rationale, References and Websites.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Revised	05/19/2011	MPTAC review.
Revised	05/18/2011	Hematology/Oncology Subcommittee review. Reformatted and clarified AML criteria. Removed redundant medically necessary statements for ALL and CLL/SLL sections. Changed “myelodysplastic disorder” to “myelodysplastic neoplasms.” Updated Rationale, References and Websites.

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## Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome

Revised	05/13/2010	MPTAC review.
Revised	05/12/2010	Hematology/Oncology Subcommittee review. Removed “high dose chemotherapy with” from title. Clarified medically necessary AML harvest criteria. Clarified investigational and not medically necessary criteria for hematopoietic stem cell harvest. Added CML criterion for “no hematologic response at 3 months”. Clarified CML criterion for T315-I mutation. Updated rationale, references and websites.
Revised	05/21/2009	MPTAC review.
Revised	05/20/2009	Hematology/Oncology Subcommittee review. Clarified title and scope to pertain to “select” leukemias. Clarified AML risk indicators. Removed “suitably matched” language from criteria. Updated rationale to include information about stem cell “boosts”. Background, references and websites and coding updated.
Revised	11/20/2008	MPTAC review.
Revised	11/19/2008	Hematology/Oncology Subcommittee review. Clarified Patient Selection Criteria. Updated websites.
	10/01/2008	Updated Coding section with 10/01/2008 ICD-9 changes.
Revised	05/15/2008	MPTAC review.
Revised	05/14/2008	Hematology/Oncology Subcommittee review. Updated rationale, background, references and websites. Updated disease classification for acute myelogenous leukemia and acute lymphoblastic leukemia.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS G0267 deleted 12/31/2007.
Reviewed	11/29/2007	MPTAC review.
Reviewed	11/28/2007	Hematology/Oncology Subcommittee review. Updated references and websites. The phrase “investigational/not medically necessary” was clarified to read “investigational and not medically necessary.”
	05/17/2007	Added note to cross reference TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation.
Revised	12/07/2006	MPTAC review.
Revised	12/06/2006	Hematology/Oncology Subcommittee review. Addition of medically necessary statement for primary graft failure; MDS classification table moved to the definition section.
Revised	06/08/2006	MPTAC review.
Revised	06/07/2006	Hematology/Oncology Subcommittee review. Revision to general patient selection criteria; addition of medically necessary indication for primary refractory AML and AML derived from MDS or MPD.
Revised	01/31/2006	Added definition of IPSS in the Definitions Section.
Revised	12/01/2005	MPTAC review.
Revised	11/30/2005	Hematology/Oncology Subcommittee. Eliminated age requirements, revised general patient selection criteria, added SLL, CMML position. Changed MPD from medically necessary to investigational/not medically necessary.
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).

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Reviewed	07/14/2005	MPTAC review.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	10/28/2004	TRANS.00002	Stem Cell Transplant following Chemotherapy for Malignant Diseases
WellPoint Health Networks, Inc.	12/02/2004	7.11.02	Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Support (PBSCS) for Malignancies
	12/02/2004	7.11.03	Allogeneic Bone Marrow or Stem Cell Transplantation
	12/02/2004	7.11.05	Mini-Transplants
	12/02/2004	7.11.06	Second Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Support (PBSCS) in Multiple Myeloma
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for AML
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for CLL
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for ALL
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for CML
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for Myeloproliferative Disorders/MDS (Myelodysplastic Syndrome)
	12/02/2004	Clinical Guideline	Second Bone Marrow/Stem Cell Treatment

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