

Facts About Hematopoietic Stem Cell Transplant (HSCT)

Introduction

Hematopoietic stem cell transplantation (HSCT) has been an integral component of blood cancer treatment for decades, with well over one million procedures performed worldwide to date. Improvements in transplant technique and supportive care have improved outcomes for patients and minimized risks to donors. However, HSCT is still associated with significant complications in the short and long term. Although survival has improved markedly over time, post-transplant mortality, often due to graft-versus-host disease (GVHD) or blood cancer relapse, remains a significant concern. This publication describes the development of HSCT and its growth over time, trends in transplantation types and stem cell source, donor selection, the HSCT process including pre- and post-transplant considerations, patient outcomes, long-term effects, and emerging trends that may lead to clinical advances. This guide also includes resources from The Leukemia and Lymphoma Society (LLS) and other organizations that provide quality information on HSCT. These resources will help healthcare providers better understand the role of HSCT in blood cancers, and will help patients, families, and caregivers as they struggle with the complexities of this treatment that is an effective yet challenging component of the cancer journey.

Note: this fact sheet focuses on the use of HSCT in adult patients (>18 years of age). For information on the use of HSCT in pediatric patients, please see “Patient and Provider Resources” section at the end of the document.

Highlights

- The use of HSCT has grown steadily over the past several decades. In 2021, more than 22,000 HSCTs performed in the US were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) research database.
- Today, HSCT is considered standard of care for a wide range of hematologic malignancies and hematopoietic system disorders, though its specific use varies according to the malignancy and disease state (e.g., whether the disease is in remission or relapse).
- Most HSCTs today are autologous (i.e., the patient’s own stem cells are used). The most commonly treated disease is multiple myeloma. A smaller but still substantial number of autologous transplants are in patients with lymphomas (both Hodgkin and non-Hodgkin lymphomas).
- HSCTs that are allogeneic (i.e., stem cells collected from a donor rather than the patient) are less common but are used in a broader range of hematologic malignancies, and most commonly in acute myeloid leukemia (AML).
- Donor stem cells are collected from a patient’s relatives, or an unrelated donor.
- Use of an autologous or allogeneic HSCT is primarily determined by the blood cancer, the same way standard chemotherapies differ by disease.
- For allogeneic HSCT, overall rates of mortality not related to relapse have fallen over time. However, treatment-related mortality (often driven by GVHD) remains a concern.
- Nevertheless, HSCT is regarded as an effective therapeutic approach with a substantial patient benefit, particularly when given early in the course of the disease.
- While outcomes once varied substantially according to donor type, today outcomes for well-matched unrelated donor transplants are considered to be on par with outcomes for sibling donor transplants.

Highlights (cont.)

- The most common stem cell source today is peripheral blood, followed by bone marrow at a distant second, and umbilical cord blood in a minority. Peripheral blood stem cells can be obtained through a relatively uncomplicated outpatient procedure, while bone marrow requires surgery under general anesthesia.
- HSCT is associated with significant acute toxicities and longer-term complications, necessitating careful monitoring over time.
- Acute and chronic GVHD remain potentially life-threatening complications of HSCT, particularly for patients with severe cases. Several targeted therapies have been approved in recent years, though there remains an unmet need for new treatments.
- Advances in the field include other cellular therapies, such as CAR T cells, that may help boost the effects of HSCT, novel agents that may improve specific aspects of the procedure such as stem cell mobilization, and new approaches to prevent or treat GVHD.

Overview of HSCT

Hematopoietic stem cell transplantation (HSCT) is a procedure involving the replacement or reconstitution of an individual's bone marrow.¹ This is accomplished via intravenous infusion of hematopoietic stem cells, which are immature cells capable of developing into any type of white blood cell, red blood cell, or platelet.² Broadly speaking, the goal of HSCT is to replace bone marrow that has been damaged or destroyed by disease. By replacing abnormal or damaged hematopoietic stem cells, HSCT reestablishes hematopoiesis, restores immunologic function, and in the case of allogeneic stem cell transplantation has a potent immunologic effect that can eradicate disease and prevent relapse in situations when chemotherapy or targeted therapy cannot.³

The HSCT procedure may also be referred to as bone marrow transplantation. However, some consider the term HSCT to be more precise, since hematopoietic stem cells can be harvested not only from bone marrow, but also from peripheral blood (i.e., blood in circulation throughout the body) and umbilical cord blood.³ Accordingly, the type of HSCT a patient receives may be identified by the source of the stem cells, i.e., bone marrow transplant (BMT), peripheral blood stem cell transplant (PBSCT), or umbilical cord blood transplant (UCBT).⁴

The two primary types of HSCT are autologous (i.e., stem cells are harvested from the same individual) and allogeneic (i.e., stem cells are harvested from a donor.). In autologous HSCTs, the patient's own stem cells are infused as a rescue strategy following the use of chemotherapy (with or without radiotherapy), which eradicates the malignancy but induces otherwise life-threatening myelosuppression.⁵ By contrast, an allogeneic procedure is more complex, involving the infusion of stem cells from a healthy, human leukocyte antigen (HLA)-compatible donor. An allogeneic HSCT establishes normal hematopoiesis and immunity, enabling a “graft-versus-tumor” effect that can help eradicate residual disease and prevent relapse (note that “graft” refers to donor derived cells).^{6,7}

A third type of stem cell transplant is syngeneic HSCT,

in which donor stem cells are taken from a monozygotic identical twin. A syngeneic transplant avoids certain risks of HSCT such as graft-versus-host disease (GVHD) and graft failure. However, it is exceedingly rare that a blood cancer patient in need of a transplant will have a twin available as a potential donor.⁸

Development of HSCT Over Time

A crucial step toward development of HSCT occurred in 1956, when researchers reported on the treatment of leukemic mice with radiation and intravenous injections of myeloid tissue or bone marrow. Results of these experiments suggested the potential of a newly engrafted immune system to prevent disease recurrence.⁹

In 1957, the seminal research article on human bone marrow transplantation was published in the *New England Journal of Medicine*. The report, written by pioneering researcher E. Donnall Thomas and co-authors, documented the effects of intravenous infusions of donor bone marrow in a series of 6 patients treated with radiation and chemotherapy. The results were encouraging, with 2 patients showing evidence of engraftment, though all died within 100 days of transplant.¹⁰

Further advances in transplant science were needed. Research linking human leukocyte antigen (HLA) to successful transplant outcomes appeared as early as 1965, when researchers showed a correlation between HLA matching and survival of kidney allografts.¹¹ In 1968, researchers reported on a successful allogeneic transplant in a 5-month old male infant with severe combined immunodeficiency (SCID) using peripheral blood and bone marrow cells from an HLA-matched sibling donor.¹²

The first evidence linking allogeneic transplantation to a possible cure of a hematologic disease was published in 1977, also by Thomas and co-authors. In this study of 100 consecutive transplantations in patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), 13 patients remained alive and without treatment at up to 4.5 years after transplantation.¹³

The first autologous bone marrow transplantation was performed in Paris in 1977 in a 28-year-old male patient with AML. Over time, the autologous stem cell transplant (ASCT) became a routine component of treatment for lymphoid malignancies.¹⁴ Starting in the mid- to late-1980s, use of autologous transplant increased substantially due to improved transplant strategies and better supportive care, making it a treatment of choice for patients with acute leukemias and relapsed lymphomas.¹⁵

Growth of HSCT in Recent Decades

With continued advances in research, both autologous and allogeneic HSCT have played an increasingly important role in the treatment of blood cancers. By December 2012, the estimated number of HSCTs performed worldwide surpassed the 1 million mark.¹⁶ In the US, the number of first HSCTs reported in 2021 exceeded 22,000, of which approximately 12,000 were autologous, according to statistics from the Center for International Blood and Marrow Transplant Research (CIBMTR). Growth in the number of autologous HSCT procedures has consistently outpaced growth in allogeneic HSCT over the past several decades (**Figure 1**).¹⁷

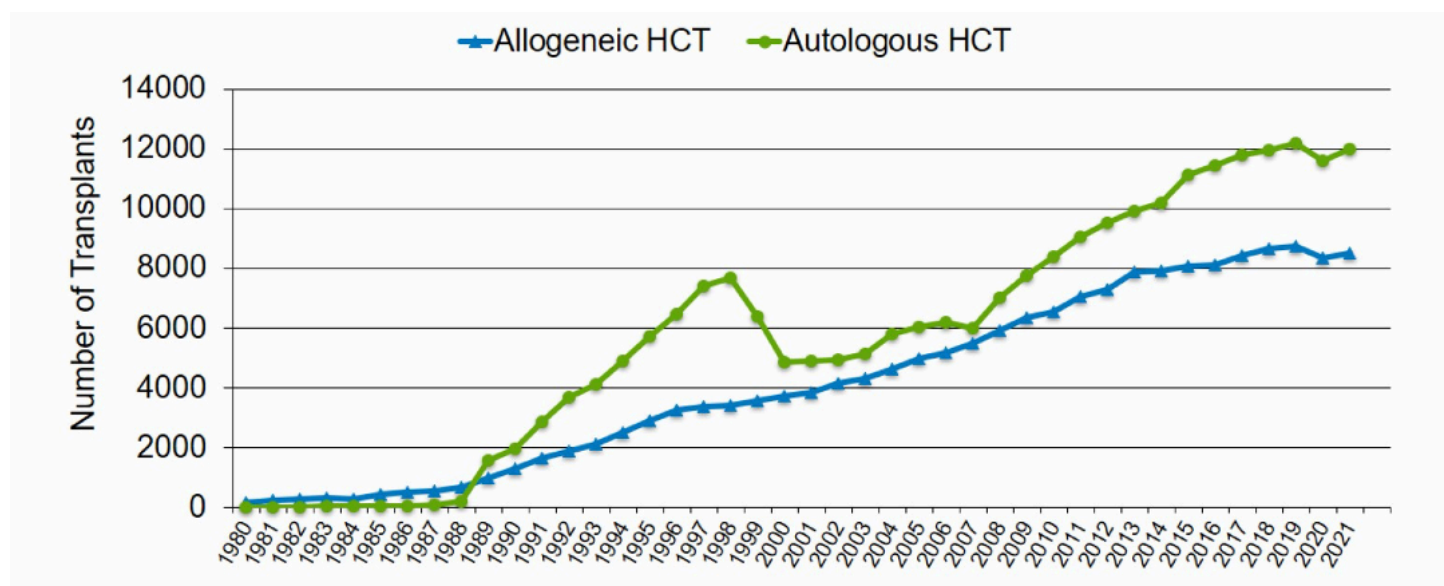


Figure 1. Number of First HSCTs Reported in the United States to the Center for International Blood and Marrow Transplant Research (CIBMTR).

Adapted from Bolon et al, CIBMTR Summary Slides.¹⁷ The views expressed in this article are those of the authors and do not reflect the position of the Center for International Blood and Marrow Transplant Research.

HSCT in Blood Cancers

HSCT today is considered a standard of care for a wide range of hematologic malignancies and hematopoietic system disorders. The use of HSCT also has been evaluated and used in genetic disorders such as hemoglobinopathies, and in some solid tumors such as testicular germ cell tumors.³

Blood cancer indications vary by type of HSCT. In adult patients, allogeneic transplants have been used predominantly in the treatment of acute leukemias, myelodysplastic syndromes, and myeloproliferative neoplasms, while autologous transplants are most commonly used in multiple myeloma and lymphomas.

Likewise, the goals of therapy differ depending on transplant type. With allogeneic HSCT, the intent of treatment is generally curative. Autologous HSCT can be curative in patients with relapsed or refractory lymphomas; by contrast, its use in multiple myeloma is not believed to be curative, but is generally regarded as an effective therapy with a survival benefit.¹⁸

In the US, the most common indication for HSCT is myeloma/plasma cell disorders, with nearly 8,000 procedures reported to the CIBMTR in 2021. A distant second and third were AML and non-Hodgkin lymphomas, with approximately 3,000 procedures each. Myelodysplastic syndromes and myeloproliferative neoplasms collectively accounted for approximately 2,000 HSCTs that year, while ALL accounted for roughly 1,000 HSCTs (Figure 2).¹⁷

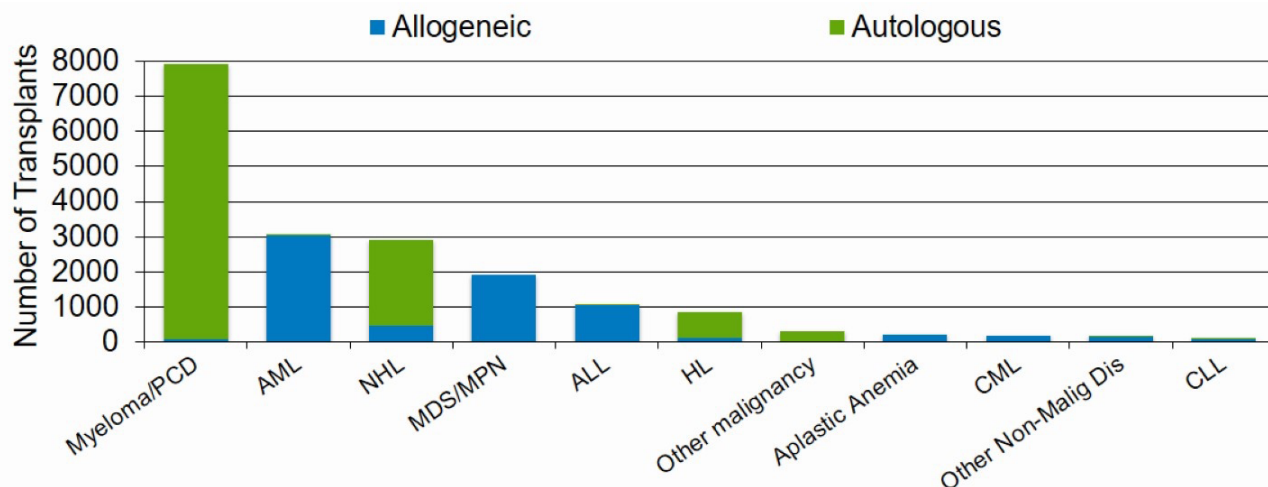


Figure 2. Number of HSCTs in US Adults in 2021.

Abbreviations: MM = multiple myeloma; PCDs = plasma cell disorders; AML = acute myeloid leukemia; NHL = non-Hodgkin lymphoma; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasms; ALL = acute lymphoblastic leukemia; HL = Hodgkin lymphoma; CML = chronic myeloid leukemia; CLL = chronic lymphocytic leukemia. Non-malignant disease category excludes aplastic anemia in adults 18 years of age or older. Adapted from Bolon et al, CIBMTR Summary Slides.¹⁷ The views expressed in this article are those of the authors and do not reflect the position of the Center for International Blood and Marrow Transplant Research.

Eligibility for HSCT

Not all patients are eligible to receive HSCT. Patients should undergo an extensive evaluation that considers factors such as overall health and performance status, comorbidities, disease status, chemosensitivity, and concurrent psychosocial issues. Some factors are donor-related, including stem cell source and donor type (related or unrelated). Others include but are not limited to: logistical concerns (such as availability of caregiver support), transplant center requirements, and access to care.^{19,20}

Although there are some absolute contraindications to HSCT such as pregnancy, liver cirrhosis, and an active second cancer, other factors such as age >65 years, performance status, and lung function are considered relative contraindications. Older age is a particularly controversial variable when considering HSCT eligibility. Instead of basing the transplant decision on chronologic age (i.e., the actual number of years a person has lived), some feel that the decision should be based on physiologic age (i.e., an “age” determined based on patient health, fitness, and function). Ultimately, the decision to proceed or not to proceed should be made by an interdisciplinary team that carefully considers patient factors, donor characteristics, and the disease itself.²¹

Indications for Autologous Transplantation

For patients with newly diagnosed multiple myeloma who are eligible for high-dose chemotherapy, the use of autologous transplantation following induction therapy is a well-established standard of care. Autologous transplantation is also recommended at the time of first progression for transplant-eligible myeloma patients who did not previously receive autologous transplantation.²² Nearly 110,000 autologous transplants in myeloma patients in the US were reported to the CIBMTR from 1990 through 2022.²³ The number of reported autologous transplants in patients with plasma cell disorders (the vast majority of which are myeloma) reached a record level in 2021, approaching 8,000 cases (Figure 3).¹⁷

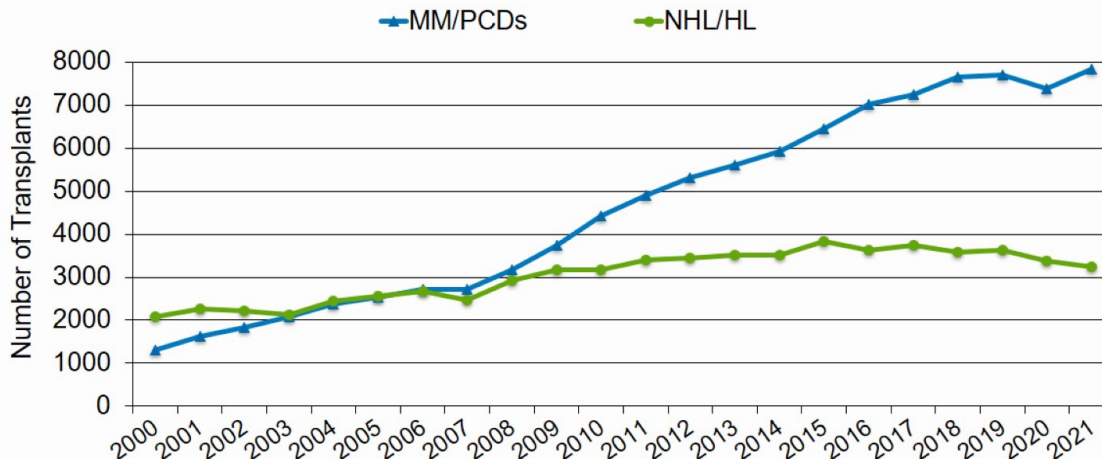


Figure 3. Autologous HSCTs in the US by Disease Type as reported to CIBMTR.¹⁷

Abbreviations: MM = multiple myeloma; PCDs = plasma cell disorders; NHL = non-Hodgkin lymphoma; HL = Hodgkin lymphoma. Adapted from Bolon et al, CIBMTR Summary Slides.¹⁷ The views expressed in this article are those of the authors and do not reflect the position of the Center for International Blood and Marrow Transplant Research.

Autologous transplantation is also indicated for certain patients with Hodgkin lymphoma, as well as non-Hodgkin lymphomas including follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) or high-grade lymphomas, mantle cell lymphoma, and other high-risk lymphomas.²⁰ Over the past decade the number of Hodgkin and non-Hodgkin lymphoma-related autologous transplants has ranged from approximately 3,000 to 4,000 per year (Figure 3).¹⁷

Indications for Allogeneic Transplantation

AML is the blood cancer most commonly treated with allogeneic HSCT. Since 2015, the number of allogeneic transplants for AML has exceeded 3,000 cases per year in the US (Figure 4). Allogeneic transplantation was first studied as a potentially curative approach for AML more than 60 years ago, and subsequent studies demonstrated its utility in adults with AML in first complete remission and other settings.^{20,24} Other blood cancers with allogeneic HSCT indications include myelodysplastic syndromes and myeloproliferative neoplasms, chronic myeloid leukemia, acute lymphoblastic leukemia, and chronic lymphocytic leukemia (Table 1).²⁰

AML	MDS	CML
<ul style="list-style-type: none"> • CR1 – except favorable risk • Antecedent hematological disease • Treatment related leukemia • Primary induction failure or relapse • Presence of minimal residual disease after initial or subsequent therapy • CR2 and beyond 	<ul style="list-style-type: none"> • Any intermediate or high IPSS score • Any MDS with poor prognostic features (i.e., treatment related, refractory cytopenias, adverse cytogenetics) 	<ul style="list-style-type: none"> • Inadequate hematologic or cytogenetic response after multiple tyrosine kinase inhibitors (TKI) • Intolerance to TKIs • Accelerated phase • Blast crisis
ALL	CLL	
<ul style="list-style-type: none"> • CR1 • Primary induction failure or relapse • Presence of minimal residual disease after initial or subsequent therapy • CR2 and beyond 	<ul style="list-style-type: none"> • High-risk cytogenetics or molecular features (deletion 17p or 11q) • Fludarabine resistant • Richter’s transformation • Poor initial response or short initial remission (recurrence within 12 mo) 	

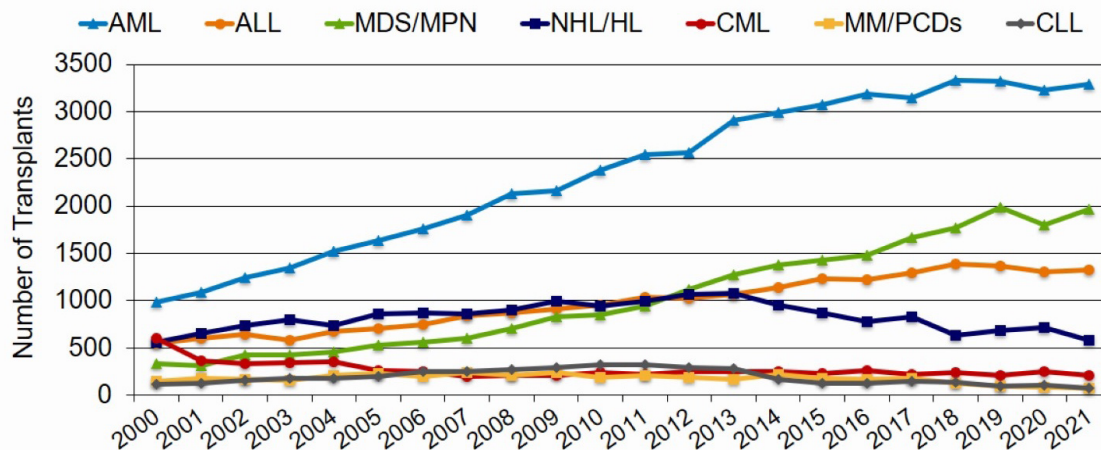


Table 1. Current Indications for Allogeneic HSCT.²⁰

Figure 4. Allogeneic HSCTs in the US by Disease Type as reported to CIBMTR.¹⁷

Abbreviations: MM = multiple myeloma; PCDs = plasma cell disorders; AML = acute myeloid leukemia; NHL = non-Hodgkin lymphoma; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasms; ALL = acute lymphoblastic leukemia; HL = Hodgkin lymphoma; CML = chronic myeloid leukemia; CLL = chronic lymphocytic leukemia. Adapted from Bolon et al, CIBMTR Summary Slides.¹⁷ The views expressed in this article are those of the authors and do not reflect the position of the Center for International Blood and Marrow Transplant Research.

HSCT Outcomes

Outcomes of HSCT have significantly improved over the past few decades due to advances in transplant techniques and supportive care.⁷ For patients undergoing allogeneic HSCT, the overall rate of non-relapse mortality at 100 days post-transplant was once as high as 30% to 40%, and now is in the range of 5% to 10%.²⁰ However, those current figures still reflect a substantial level of treatment related-mortality, driven by GVHD, complications due to infections, and toxicity related to conditioning regimens.²⁵ Furthermore, mortality due to disease progression remains a major challenge, particularly as patients may have limited treatment options post-transplant relapse.

The primary causes of mortality today vary by HSCT type. In autologous transplant, early mortality is now rare, ranging from less than 1% to 2% at most centers, and the primary cause of mortality is disease relapse. When non-relapse mortality is seen following autologous transplant, infection is often the cause.²⁰ By contrast, non-relapse mortality is more common in allogeneic HSCT, but patient populations are heterogeneous. Current mortality rates at 100 days post-transplant can be low, e.g., 7% for acute leukemia patients in remission with a matched related donor; or can be high, e.g., 27% for patients with refractory acute leukemia and a matched unrelated donor.⁷ Of particular concern is mortality related to GVHD, with a risk that increases with degree of HLA mismatch.²⁰

Although outcomes vary by transplant type and disease state, HSCT is generally regarded as an effective therapeutic approach that provides a substantial benefit, particularly

when given early in the disease course. According to the National Marrow Donor Program, transplants in patients with early disease cut the risk of mortality in half (0.53 hazard ratio) as compared to transplants in patients with advanced disease.²⁶ As such, referral for HSCT consultation is a critical factor in optimizing outcomes and taking advantage of a potentially narrow window of opportunity to proceed with HSCT. Healthcare providers are advised to consult recently published guidelines from the NMDP to determine the optimal window for referral timing based on the indication and the patient’s disease characteristics.²⁷

Factors such as older age and donor type have been associated with poorer HSCT outcomes. However, older age is not necessarily a contraindication to HSCT due to advances such as reduced intensity conditioning regimens and better post-transplant care.²⁸ The proportion of patients over 65 make up an increasingly larger proportion of allogeneic HSCT recipients each year, growing from 4% of the procedures in 2005 to 29% in 2021. Similarly, the percentage of autologous HSCTs in the over-65 age group has grown from 18% to 38% over the same time period.¹⁷

While outcomes once varied substantially according to donor type (i.e., unrelated versus sibling donors), improvements in HLA typing and other advances have closed the gap. Today, disease relapse and survival outcomes for unrelated donor transplants are considered comparable to outcomes in sibling donor transplants. CIBMTR data indicate that following unrelated donor transplantation 1-year survival improved from 43% to 66% over the course of 15 years (Table 2).²⁹

Improved Survival with Unrelated Transplantation

YEAR OF HCT	ONE-YEAR SURVIVAL
2013-2015	66%
2010-2012	61%
2007-2009	59%
2004-2006	50%
2001-2003	45%
1998-2000	43%

Table 2. Improved Survival with Unrelated Transplantation (1st Allogeneic HSCT) at US Transplant Centers. Adapted from National Marrow Donor Program. Unrelated vs. Sibling Donor Outcomes. <https://bethematchclinical.org/transplant-indications-and-outcomes/additional-outcomes/unrelated-vs--sibling-donor-outcomes/>²⁹

Hematopoietic Cell Sources

Although stem cell grafts can be obtained from several sources, today the most common source in adult patients receiving autologous or allogeneic HSCT is peripheral blood, followed by bone marrow at a distant second, and cord blood in a minority of cases. Among allogeneic HSCTs, the proportion of related and unrelated donor transplants utilizing peripheral blood is similar (roughly 8 in 10 cases). Marrow is somewhat more commonly used in related donor transplants. Umbilical cord blood is rarely used in related donor transplants and used infrequently in unrelated donor transplants (Table 3).^{17,30}

	Peripheral Blood	Marrow	Cord Blood
Related Donor	77%	23%	<1%
Unrelated Donor	80%	13%	7%

Table 3. Stem Cell Donor Sources, US Related vs Unrelated Donor Transplants; 2021. Adapted from Health Resources & Services Administration (HRSA). Donation and Transplantation Statistics.³⁰

Over time, the collection of peripheral blood stem cells has become predominant in part due to its safety to the donor and favorable survival outcomes in patients receiving the transplant.⁷

The relative benefits of the peripheral blood stem cell collection in comparison to bone marrow stem cell harvest have also driven uptake. The former can be done as an outpatient procedure, similar to a dialysis session, with cells collected using an apheresis catheter and CD34+ cell counts done using flow cytometry. By contrast, bone marrow stem cell harvest is a surgical procedure usually performed in an acute care setting under general anesthesia.^{20,31}

Recovery time is shorter for peripheral blood stem cell donors as compared to bone marrow donors. Peripheral blood collection is associated with lower rates of donor morbidity, though the complication rate of bone marrow collection is also relatively low, with serious adverse events reported in less than 0.3% of cases. In addition, bone marrow stem cell collection has been associated with slower neutrophil and platelet engraftment.^{20,31}

However, peripheral blood collection can also have drawbacks. It is required that stem cells be mobilized from the bone marrow into the bloodstream prior to collection using agents such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), or plerixafor.³² The procedure usually takes several hours but may take several days in order to collect the minimum number of cells. Placement of a large double lumen catheter may be required. Furthermore, patients may have reactions to the citrate-based anticoagulant used in apheresis.^{20,31}

Umbilical cord blood is most often donated through public banks that are anonymous, and less often from direct family members. The blood is collected from umbilical cord vessels at the time of placenta delivery. Cord blood allows for less stringent matching of HLA between the donor and recipient, and is associated with lower risk of GVHD. However, some observed disadvantages include delayed engraftment and graft failure, as well as more infectious complications and higher costs.^{20,33}

Donor Selection

The number of donors and cord blood units are continually increasing worldwide, with more than 40 million donors and more than 800,000 cord blood units on record at present.³⁴ The National Marrow Donor Program registry now includes more than 9 million potential donors in the US, of whom 3.9 million are from racial/ethnic backgrounds other than non-Hispanic white. Also on the registry are approximately 268,000 cord blood units, of which 136,000 are from diverse racial/ethnic backgrounds, expanding the access of transplantation to all populations.³⁰ Umbilical cord blood HSCT uses stem cell grafts from public cord blood banks. Use of stem cells from private cord blood banks is not standard.

HLA Typing and Matching

The degree of HLA matching is considered the most important factor in stem cell donor choice. When allogeneic transplant is a potential treatment option, the patient and potential donors in the family should undergo HLA typing. Outcomes of HSCT are directly correlated to the degree of HLA matching between the donor and recipient.²⁷

HLA mismatch is associated with increased acute and chronic GVHD, treatment-related mortality, and overall survival.³⁵ Current evidence suggests that in unrelated donor HSCTs, recipients matching for the HLA-A, -B, -C, and HLA-DRB1 alleles using high-resolution typing (8/8 matched) have improved overall survival and decreased transplant-related mortality. When an 8/8 match is not available, a 7/8 match (i.e., a single locus mismatch) can be considered.³⁶

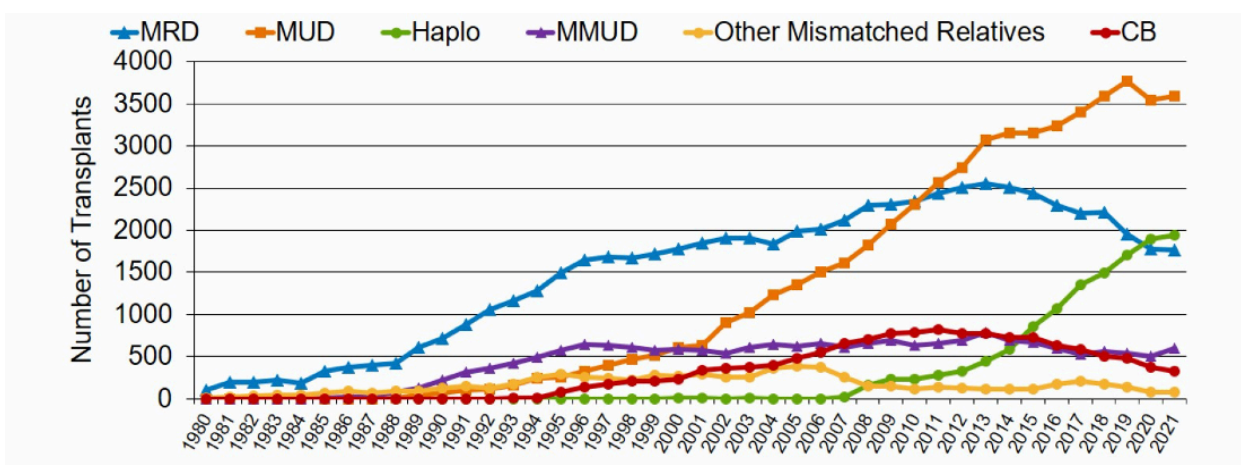
Donor Types

The ideal donor for allogeneic HSCT in adults is a sibling with an HLA genotype that is identical to the patient. However, such a donor exists in only about 30% of cases. The odds of finding a donor varies by racial/ethnic group and is lowest in Black or African American patients.³⁷ The majority of patients will require consideration of alternative stem cell sources such as a matched unrelated donor, a mismatched unrelated donor, a haploidentical donor (meaning a first-degree relative that is half matched), or a unit of cord blood.³⁸

The use of allogeneic HSCT has been extended dramatically through the use of matched unrelated donors and partially matched related donors.⁷ For decades, matched related donor transplant was the most common type of allogeneic HSCT. Since 2010, matched unrelated donor transplants have been the most common, increasing in number from approximately 2,500 to more than 3,500 from 2011 to 2021. The number of haploidentical donors has also been increasing, while by contrast, the number of cord blood transplants has been declining (Figure 5).¹⁷

Figure 5. US Allogeneic HSCTs by Donor Type, 1980-2021.¹⁷

Abbreviations: MRD = matched related donor; MUD = matched unrelated donor; Haplo = HLA antigen mismatch of 2 or more; MMUD = mismatched unrelated donor, i.e., 7/8 HLA allele match or lower; CB = cord blood. Adapted from Bolon et al, CIBMTR Summary Slides.¹⁷ The views expressed in this article are those of the authors and do not reflect the position of the Center for International Blood and Marrow Transplant Research.



HSCT Process for Patients with Blood Cancers

The process of HSCT can be broadly divided into three main phases: pre-transplant, transplant, and post-transplant. In the pre-transplant phase, patients typically undergo conditioning chemotherapy to eradicate disease and create space for engraftment. Prophylaxis to guard against infection and GVHD are important in this phase. The transplant phase itself involves the infusion of stem cells. In the post-transplant phase, the patient is monitored carefully for engraftment, as well as for complications including GVHD, graft failure, and disease relapse.

The HSCT process can be associated with significant acute toxicities and longer-term complications, necessitating careful patient monitoring over time. Inpatient hospitalization typically starts at the time of the conditioning regimen and goes until the resolution of acute toxicities seen post-engraftment. During the early ambulatory phase, which may span about 30 days for autologous transplant and about 100 days for allogeneic transplant, visits may be scheduled 1-3 times per week, depending on the patient's complications. The frequency of visits typically declines to monthly for the remainder of the first year after HSCT. During this time, care usually transitions away from specialized cellular therapy centers to the primary oncology team, necessitating careful coordination and clear communication with the patient.²⁰

Conditioning Regimens

Prior to HSCT, most patients will receive a conditioning regimen consisting of chemotherapy, immunotherapy, and/or radiation therapy.³⁹ The specific regimens vary according to blood cancer type and setting. In general, conditioning regimens are generally grouped into 3 categories based on their level of intensity:²⁰

- Myeloablative: high-intensity regimens that usually cause irreversible pancytopenia. These regimens require stem cells to restore the function of bone marrow and prevent death related to aplasia.
- Reduced-intensity conditioning: intermediate regimens that are often ablative but much less intensive than standard conditioning regimens.
- Non-myeloablative: regimens that result in moderate or minimal cytopenias.

The goal of myeloablative treatment is to eradicate the cancer and (in the case of allogeneic transplant) induce the immunosuppression to allow for engraftment.⁴⁰ By contrast, regimens that are considered reduced-intensity or non-myeloablative have fewer toxicities and complications as compared to myeloablative treatment, yet with similar rates of overall survival over the long term.⁴¹

The choice of conditioning regimen is nuanced, and made by the transplant team at time of patient evaluation, based on considerations such as disease type and stage, patient age, and performance status. Of note, less-intensive regimens have helped expand HSCT eligibility to older patients, including those 75 years of age or older.¹⁷

Stem Cell Infusion

Shortly after completing the conditioning regimen, the patient will receive the infusion of hematopoietic stem cells (sometimes referred to as “Day Zero”). The process may 30 to 60 minutes but can be longer depending on patient response and volume of cells infused.⁴²

If cells were stored prior to the infusion, they may have been frozen using dimethyl sulfoxide (DMSO) as a cryoprotectant. DMSO produces a characteristic garlic-like odor and taste, and may also induce histamine release, leading to a range of side effects such as nausea and vomiting, headache, flushing, fever, and dyspnea, and rarely, more serious complications including bradycardia. Accordingly, premedication with an antihistamine may be used to prevent reactions.⁴³

While blood type compatibility is crucial to solid organ transplantation, up to half of HSCTs are mismatched for A, B, and O blood groups. As a consequence, patients may experience immediate (or delayed) hemolytic complications, the risk of which can be ameliorated by graft manipulation and apheresis techniques.⁴⁴

Engraftment

Patients should also be monitored for successful engraftment (which usually occurs within 30 days of transplant) and hematopoietic chimerism. Rising white blood cell counts are an early sign engraftment. Commonly, engraftment is considered to be achieved when the patients experiences the first of three consecutive days of sustained peripheral blood neutrophil count $>500 \times 10^6/L$.⁴⁵ Analysis of chimerism helps to document the success of HSCT. Results of the analysis may signal impending graft rejection or recurrence of the underlying disease.⁴⁶ Chimerism is considered complete when only the donor’s genotype is detected, and mixed when both donor and recipient genotypes are detected.⁴⁷

Donor lymphocyte infusion (DLI), which involves the infusion of donor T cells, may be employed to treat incomplete engraftment or as a pre-emptive measure to prevent relapse (e.g., if the chimerism level is persistently low or drops). DLI may also be used in some cases to treat relapse after HSCT.⁴⁸

Post-Transplant Monitoring and Support

After transplant, patients should be monitored for a wide range of complications, including GVHD, and for disease relapse. Patient follow-up and monitoring in the post-transplant phase should be conducted by a multidisciplinary team of healthcare professionals who have specialization and expertise in HSCT and its complications.⁷

A variety of complications may be seen in the post-transplant phase. Patients are susceptible to nausea, vomiting, and diarrhea, cytopenias, infection, and complications of special concern that include GVHD (acute and chronic), graft failure, and disease relapse. Organ injuries or toxicities may be seen, including veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS); bronchiolitis obliterans, which is typically a late manifestation of chronic GVHD, and thrombotic microangiopathy (TMA).²⁰

Infection is a major cause of morbidity and mortality post-HSCT. Risk of infection depends on a variety of factors including those that are related to the patient (e.g., older age, obesity, diabetes mellitus), the disease and its treatment (e.g., type of malignancy, prior therapies), and the transplant itself (e.g., type of transplant and stem cell graft, conditioning regimen, donor type).⁴⁹ The emergence of GVHD post-transplant also increases infection risk. While patients are more susceptible to all types of infections post-HSCT, elevated risks are notable for cytomegalovirus, fungal, and pneumococcal infections.⁵⁰ Infection prevention practices should be based on well-established principles in clinical practice guidelines, including guidelines jointly published by the Centers for Disease Control and Prevention, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation.⁵¹

Hematopoietic support is an important consideration in the peri- and post-transplant period. The primary blood products transfused in the peri-transplant period are red blood cell (RBC) and platelet concentrates.⁵² For hemodynamically stable patients, an RBC transfusion threshold of 7–8 g/dL hemoglobin is recommended. Importantly, RBCs need to be compatible with both

the stem cell donor and recipient.⁵² Growth factors (both G-CSF and GM-CSF, but predominantly G-CSF) are used post-HSCT to shorten duration of neutropenia, but it remains unclear to what extent this practice has a clinically meaningful impact on post-transplant outcomes.⁵³

Graft-Versus-Host Disease (GVHD)

Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality in patients who undergo HSCT. This systemic disorder occurs when graft immune cells (i.e., donor derived cells) identify the host (i.e., the stem cell recipient) as foreign and mount an attack on healthy, normal tissue.⁵⁴ It is estimated that GVHD occurs in approximately 30% to 50% of patients, with 14% to 36% developing severe acute GVHD.²⁰

The prognosis is poor for patients with severe cases of acute GVHD, with long-term survival (>2 years) seen in only 25% to 30% of grade III cases and just 1% to 2% of grade IV cases. In addition, 30% to 70% of patients will have some chronic GVHD.²⁰ Patients with GVHD also have decreased quality of life, increased health care costs, and longer hospital stays compared to patients with no GVHD.⁵⁵

Acute GVHD often manifests as rash, gastrointestinal, and liver involvement, while chronic GVHD affects multiple organ systems, including skin, eye, mouth, liver, lung, gastrointestinal, and musculoskeletal system.^{56,57}

Initial treatment for acute GVHD is typically a systemic corticosteroid such as prednisone. However, efficacy is often incomplete, as patients may go on to develop steroid-refractory disease, and prolonged steroid therapy is associated with complications, morbidity, and mortality.⁵⁸ Topical corticosteroids and tacrolimus may be used to treat mild cutaneous acute GVHD. Systemic corticosteroids (commonly, prednisone at 1 to 2 mg/kg/day starting dose) are the long-standing standard initial therapy for more advanced cases. Limitations of this practice include incomplete efficacy, risk of complications with prolonged steroid therapy, and the potential emergence of steroid-refractory disease. Today, a second-line option for treating acute GVHD is ruxolitinib, a selective inhibitor of Janus kinase (JAK)1 and JAK3.⁵⁹ Other treatment options are needed beyond second line therapy.⁶⁰

Chronic GVHD is also treated according to severity. Mild cases may be amenable to localized, topical treatments, while moderate-to-severe chronic GVHD is typically treated with systemic corticosteroids, with or without calcineurin inhibitors.⁶¹ Current options for steroid-refractory chronic GVHD are wide-ranging with use supported based on varying levels of clinical evidence. Targeted therapies, specifically FDA-approved for use in this setting, include the Bruton tyrosine kinase inhibitor, ibrutinib, and the ROCK2 pathway inhibitor belumosudil. Ibrutinib was approved for adult and pediatric patients (1 year of age and older) with chronic GVHD after failure of at least one prior line of systemic therapy.⁶² Belumosudil is indicated for adult and pediatric patients 12 years of age and older with chronic GVHD following failure of 2 or more lines of therapy.⁶³

Patient Care Considerations During HSCT

The complexity of care during HSCT delivery presents challenges that can lead to suboptimal patient management or delays in care.⁶⁴ Providing coordinated patient care during HSCT requires the collaboration of physicians, nurses, advanced practitioners, and other providers representing multiple clinical specialties, including but not limited to transplant, transfusion services, infectious disease, intensive care, primary care, pharmacy, social work, case management, and nutrition.⁶⁴

The majority of the HSCT process, from receipt of preparative chemotherapy regimens through supportive care during hematopoietic recovery, takes place entirely in hospital settings. Patients can expect a hospital stay of approximately 14 days in the case of autologous transplantation and approximately 30 days for allogeneic transplantation.⁶⁵

Throughout the HSCT procedure and acute follow-up period, special precautions should be undertaken to prevent opportunistic infections.⁶⁶ Transplant recipients need to be situated in properly ventilated rooms, and guidelines for hospital isolation practices need to be adhered to throughout the HSCT unit. Hand hygiene is the single best preventive measure against nosocomial infections, so proper hand-washing practices should

be emphasized to staff, patients, caregivers, and visitors. Screening of visitors for potentially infectious conditions (especially children) should be conducted by clinically trained healthcare personnel.⁶⁶

For the patient, this prolonged period of care can be stressful and even traumatic. Patients undergoing HSCT high prevalence of psychological distress, which can have negative implications for recovery and clinical outcomes following the procedure. Depression, delirium, and post-traumatic stress reactions are several common challenges patients may experience during HSCT hospitalization that may warrant psychiatric consults, behavioral intervention, and pharmacologic treatment.⁶⁷ The patient's transplant caregiver, typically a spouse/partner, brother or sister, adult child, friend, or coworkers, may also be overwhelmed and unsure how to best provide support. A variety of resources are available to assist healthcare providers in offering guidance, education, and support to patients and their caregivers during this time (see the *Patient and Provider Resources* section of this LLS Fact Sheet).

Long-term Effects and Late Complications

Today, there are many thousands of HSCT survivors being followed for care, providing important data on complications over time. Increased awareness of these issues is needed to ensure that patients are carefully managed to minimize morbidity and optimize outcomes.⁶⁸

In addition to chronic GVHD, individuals who have undergone HSCT can experience late effects such as toxicities due to the treatment regimen, infections secondary to immunodeficiency, impairment of growth, infertility endocrine disturbances (notably hypothyroidism), secondary malignancies, and psychosocial distress, among other issues.⁶⁸

Late and long-term effects of HSCT are complex, unpredictable, and often influenced by multiple factors related to the patient's health status. Accordingly, individuals who successfully undergo HSCT require consistent care and regular evaluations informed by stringent, well-established protocols. At the same time, the case needs to be individualized based on the needs of each patient.⁶⁹

Emerging Trends

Combining other cellular therapies with HSCT may help boost the recipient's immune system to more effectively fight disease and infection.⁷⁰ For example, growing evidence suggests that chimeric antigen receptor (CAR) T-cell therapy given prior to allogeneic HSCT in pediatric ALL may improve response rates, prolong remission, and reduce relapse rates as compared to CAR T-cell therapy alone.⁷¹

Other emerging cellular treatments with the potential to promote immunity by boosting HSCT include cells that incorporate both a CAR against the disease and a natural killer (NK) inhibitory CAR, OX40-specific cytotoxic T lymphocytes combined with CAR T cells, and a novel cellular therapy that consists of enriched CD34+ stem cells combined with specific T-cell subsets.⁷⁰

Advances are needed in other aspects of HSCT. For example donor stem cell mobilization is not always successful with current mobilization regimens that incorporate growth factors or plerixafor. Newer mobilizing regimens that incorporate novel agents, either alone or in combination with G-CSF and plerixafor, may improve collection efficacy while decreasing procedure-related risks such as thrombocytopenia and infection.⁷²

In addition, there have been numerous approaches developed, most experimental, that may help in the prevention or treatment of GVHD such as inhibition of T cell signaling, stem cell graft engineering, and adoptive regulatory T (Treg) cell therapy.⁷³ The targeting antigen-presenting cells, lymphocytes, or GVHD neovascularization are several treatment approaches under investigation to potentially slow or halt the pathogenic reaction of donor lymphocytes against normal cells.⁷⁴

Patient and Provider Resources

For Healthcare Providers

- National Marrow Donor Program (NMDP) US Summary Slides - HCT Trends and Survival Data <https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports>
- National Marrow Donor Program (NMDP) Transplant Center Search - Select a state or enter the patient's diagnosis to search for transplant centers. <https://bethematch.org/tcdirectory/search/>
- Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR <https://ashpublications.org/blood/article/134/12/924/374909/Selection-of-unrelated-donors-and-cord-blood-units>
- Post-Transplant Guidelines (CIBMTR) <https://cibmtr.org/CIBMTR/Utility-Nav/Patients/Post-Transplant-Guidelines>
- The EBMT Handbook, 7th edition: Hematopoietic Stem Cell Transplantation and Cellular Therapies <https://www.ncbi.nlm.nih.gov/books/NBK553942/>
- Pediatric Hematopoietic Stem Cell Transplantation and Cellular Therapy for Cancer (PDQ®)–Health Professional Version <https://www.cancer.gov/types/childhood-cancers/hp-stem-cell-transplant>

For Patients, Families, and Caregivers

- American Cancer Society - Stem Cell or Bone Marrow Transplant <https://www.cancer.org/cancer/managing-cancer/treatment-types/stem-cell-transplant.html>
- Be The Match (National Marrow Donor Program)
 - Patients and Families <https://bethematch.org/patients-and-families/>
 - Caregiver Resources <https://bethematch.org/patients-and-families/caregivers-and-transplant/>
- Stem Cell Transplant: Guides for Patients & Caregivers (Memorial Sloan Kettering Cancer Center)
 - Autologous HSCT: <https://www.mskcc.org/cancer-care/patient-education/autologous-stem-cell-transplant-guide-patients-caregivers>
 - Allogeneic HSCT: <https://www.mskcc.org/cancer-care/patient-education/allogeneic-stem-cell-transplantation>
- National Bone Marrow Transplant Link (NBMT Link) NEW Online Resource Guide: an interactive guide of organizations that provide helpful information and support for cancer/transplant patients and their loved

ones. <https://www.nbmtlink.org/helpful-resources/>

- My Child is Having a Transplant (Anthony Nolan) <https://www.anthonynolan.org/patients-and-families/support-parents-family-and-friends/my-child-having-a-transplant>
- Transplant for Children and Teens <https://bethematch.org/patients-and-families/transplant-for-children-and-teens/>

LLS Resources

- Leukemia & Lymphoma Society (www.LLS.org)
- Stem Cell Transplantation – Overview <https://www.lls.org/treatment/types-treatment/stem-cell-transplantation>
- Blood and Marrow Stem Cell Transplantation Guide <https://www.lls.org/booklet/blood-and-marrow-stem-cell-transplantation-guide>
- Blood and Marrow Stem Cell Transplantation Booklet <https://www.lls.org/booklet/blood-and-marrow-stem-cell-transplantation>
- Cord Blood Stem Cell Transplantation https://www.lls.org/sites/default/files/file_assets/cordbloodstemcelltransplantation.pdf

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has regions throughout the United States and Canada. To find the region nearest to you, visit our website at www.LLS.org/ChapterFind or contact

The Leukemia & Lymphoma Society

3 International Drive, Suite 200
Rye Brook, NY 10573
Phone Number: (800) 955-4572
(M-F, 9 a.m. to 9 p.m. ET)
Website: www.LLS.org

LLS offers free information and services for patients and families touched by blood cancers as well as for healthcare professionals. The resources listed below are available to you and your patients.

Consult with an Information Specialist. Information Specialists are highly trained social workers and nurses who assist through treatment, financial, and social challenges. They offer up-to-date disease and treatment information.

Language services are available.

For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. ET)
- Visit: www.LLS.org/IRC
- Contact: www.LLS.org/form/contact-us
- Live chat: www.LLS.org/informationsspecialists

Clinical Trials Support Center (CTSC). Work one-on-one with an LLS clinical trial nurse navigator who will personally assist throughout the entire clinical trial process. A nurse navigator will help identify potential clinical trials and overcome the barriers to enrollment (navigators help HCPs and patients). For more information about this free service, please

- Call an Information Specialist: (800) 955-4572 to be referred to the CTSC
- Visit: www.LLS.org/CTSC

- Complete a referral form for your patient at: www.LLS.org/CTSCreferral

Nutrition Consultations. Nutrition Education Services Center (NESC) provides one-on-one **free** nutrition education and consultations to patients and caregivers of all cancer types with registered dietitians who have expertise in oncology nutrition.

- Visit: www.LLSnutrition.org

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit: www.LLS.org/booklets.

Información en Español. (LLS information in Spanish.) Para mayor información por favor visite: www.LLS.org/espanol.

LLS Community. LLS Community is an online social network and registry for patients, caregivers, and healthcare professionals. It is a place to ask questions, get informed, share your experience, and connect with others. To join visit: www.LLS.org/community

LLS Regions. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your region, please

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Patti Robinson Kaufmann First Connection® Program.

A free peer-to-peer support program that connects patients and their loved ones to a trained peer volunteer who has gone through a similar experience.

- www.LLS.org/FirstConnection

LLS Website. www.LLS.org/treatment/types-treatment/stem-cell-transplantation

Resources for Healthcare Professionals: webinars, podcasts, in-person education programs, videos, and fact sheets:

- www.LLS.org/CE (offering free accreditation)
- www.LLS.org/HCPpodcast
- www.LLS.org/HCPvideos
- www.LLS.org/HCPbooklets

Resources for you Patients:

- www.LLS.org/programs
- www.LLS.org/EducationVideos
- www.LLS.org/podcast

Additional Resource

The National Cancer Institute (NCI)

www.cancer.gov

(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer. The NCI also provides a clinical trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where healthcare professionals and patients can look for clinical trials.

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