LEUKEMIA & LYMPHOMA SOCIETY®

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Acute Lymphoblastic Leukemia in Adults

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A six-word narrative about living with blood cancer from patients in our LLS Community

Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/ happy I'm alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith, nutrition and optimism. Finding the joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.

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Join our online social network for people who are living with or supporting someone who has a blood cancer. Members will find:

- **Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff**
- **Accurate and cutting-edge disease updates**
- **The opportunity to participate in surveys that will help improve care.**

Inside This Booklet

Acknowledgement

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Introduction

This book provides information for patients and their families about acute lymphoblastic leukemia (ALL) in adults. Acute lymphoblastic leukemia is also known as “acute lymphocytic leukemia” and “acute lymphoid leukemia.”

People of all ages, from infancy to the elderly, can develop ALL. This book discusses ALL in adults and includes information on young adults. For more information about ALL in children, **visit www.LLS.org/booklets to see the free LLS book, *Acute Lymphoblastic Leukemia in Children and Teens.***

While this book focuses on acute lymphoblastic leukemia (ALL), there is a type of non-Hodgkin lymphoma, called “acute lymphoblastic lymphoma.” This type of lymphoma starts in the same kind of cells that cause ALL. Patients with acute lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens, rather than traditional lymphoma therapy. So, if you have been diagnosed with acute lymphoblastic lymphoma, this book may also be helpful for you.

At The Leukemia and Lymphoma Society (LLS), we believe that the more you know about your disease, the better you can take care of yourself, your mind, your body and your health. This book provides information about ALL, explains tests and treatments for the disease and lists treatment options. It also provides information about clinical trials, normal blood and bone marrow, and defines hard-to-understand terms. Additionally, there is information about mixed phenotype leukemia (MPAL), a combination of two forms of leukemia; acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).

We trust that this information will provide you with a good working knowledge about ALL or that it reinforces what you already know. We hope you will keep this book handy and, should you ever feel alone when confronting problems, you will turn to it for information and guidance to locate the support and resources you need. You can also contact us directly at at (800) 955-4572.

We are here to help.

All LLS publications mentioned in this booklet are free and can be viewed, downloaded or ordered online at www.LLS.org/booklets.

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Leukemia

Leukemia is a type of cancer. Cancer is a term for diseases in which abnormal cells grow uncontrollably and can spread to other parts of the body. Cancer can start almost anywhere in the body. Leukemias are cancers that begin in cells that would normally develop into blood cells.

Most blood cells are made in the bone marrow. Bone marrow is the spongy tissue in the center of most bones. There are three main types of blood cells: red blood cells, white blood cells and platelets. Red blood cells carry oxygen throughout the body. White blood cells help fight infections. Platelets help stop bleeding by clotting (clumping together) at the site of an injury.

Inside the bone marrow, there are blood stem cells, called "hematopoietic" stem cells, which are immature cells that can develop into different types of blood cells. A blood stem cell goes through many stages before it eventually develops into a red blood cell, a white blood cell or a platelet.

Leukemia begins in one of the immature blood cells in the bone marrow. One or more mutations (changes) occur in the DNA of the cell, and it becomes a type of cancer cell, called a "leukemia cell."

Leukemia cells do not mature into healthy, functioning blood cells. They grow more quickly and live longer than normal blood cells. They divide and copy themselves to make more and more leukemia cells. Over time, the leukemia cells crowd out and suppress the development of normal, healthy blood cells in the bone marrow, and they spill out of the bone marrow into the bloodstream.

The four major types of leukemia are:

- Acute lymphoblastic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)
- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML)

Doctors classify leukemia based on disease progression (meaning how quickly the disease gets worse) and the type of blood cells involved. Leukemias can be "acute" or "chronic." Acute leukemias develop and progress rapidly and usually get worse quickly if they are not treated. Chronic leukemias usually progress more slowly.

Leukemia is also classified by the type of blood cell that becomes cancerous. Blood stem cells develop into two primary types: lymphoid and myeloid. Lymphoid stem cells eventually become a type of white blood cell called "lymphocytes." Myeloid stem cells eventually become red blood cells, platelets, or other types of white blood cells (basophils, eosinophils, monocytes and

neutrophils). Leukemia is called “lymphocytic” or “lymphoblastic” if the cancerous change begins in a lymphoid cell. Leukemia is called “myeloid” or “myelogenous” if the cancerous cell change starts in a myeloid cell.

For general information about ALL, visit www.LLS.org/booklets to see the free LLS book *The ALL Guide: Information for Patients and Caregivers.*

Acute Lymphoblastic Leukemia

How Acute Lymphoblastic Leukemia (ALL) Develops. ALL is a type of cancer in which the bone marrow makes too many immature lymphocytes, a type of white blood cell. Lymphocytes begin in the bone marrow as a lymphoid stem cell. A lymphoid stem cell becomes a lymphoblast that eventually develops into a lymphocyte (white blood cell). There are three major types of lymphocytes: B cells, T cells and NK cells.

In people with ALL, a mutation (or a series of mutations) in the DNA (genetic material) of the lymphoid stem cell results in the formation of leukemic lymphoblast that is stuck in the earliest stage of cell development. This leukemia cell, also referred to as an "All blast" or "ALL cell," cannot mature into a fully functioning lymphocyte that helps fight infection.

Genetic errors in the lymphoblast cause the cell to keep growing and dividing, whereas a healthy cell would stop dividing and eventually die. In leukemia, every cell that arises from the initial leukemia blast cell also has mutated DNA. As the leukemia cells multiply uncontrollably and quickly accumulate in the bone marrow, they slow down or stop the production of normal, healthy red blood cells, white blood cells and platelets. As a result, there are too many immature lymphoblasts that cannot fight infections and too few mature, functional red blood cells, white blood cells and platelets.

Over time, the leukemia cells spill out of the bone marrow into the bloodstream. This can cause the number of white blood cells in the blood to increase, but most of these are leukemia cells that do not protect against infection. Once in the blood, the leukemia cells can spread to other parts of the body such as the central nervous system (brain and spinal cord), or the testicles in males.

By the time ALL is diagnosed, the number of healthy red blood cells, white blood cells and platelets is usually lower than normal. Having low levels of these normal cells may result in anemia, infections, and excessive bleeding or bruising.

Medical term:	Description:
Anemia	Low red blood cell count
Thrombocytopenia	Low platelet count ("thrombocyte" is another word for platelet)
Neutropenia	Low neutrophil count (a neutrophil is a type of white blood cell)

This book focuses on ALL, but there are other cancers, called "lymphomas," that also begin in lymphoid cells. Most lymphomas arise from more mature lymphoid cells, but in rare instances they can develop from lymphoblasts. The main difference between lymphoblastic leukemia and lymphoblastic lymphoma is the location of the cancer cells. Leukemias such as ALL generally affect the bone marrow and the blood. In contrast, lymphomas are mostly located in lymph nodes or other lymphatic tissues or organs such as the spleen. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy.

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of disease. A "sign" is a change that the doctor sees during an exam or in a laboratory test result. A "symptom" is a change that a patient can see and/or feel.

A person who has signs or symptoms that suggest the possibility of leukemia is referred to a specialist called a hematologist-oncologist. This is a doctor who has special training in diagnosing and treating blood disorders and blood cancers such as leukemia, lymphoma and myeloma.

It is common for someone with ALL to feel a loss of well-being because of the lack of normal, healthy blood cells. This happens when the leukemia cells in the bone marrow crowd out the normal blood-making cells. Consequently, patients with ALL may not have enough mature red blood cells, white blood cells and/or platelets, and often have symptoms related to low blood cell counts.

Symptoms of anemia (low red blood cell count) include:

- Fatigue
- Shortness of breath during normal physical activities
- Dizziness
- Pale complexion

Symptoms of neutropenia (low number of neutrophils, a type of white blood cell important in fighting infections) include:

- Frequent infections
- Fever

Symptoms of thrombocytopenia (low platelet count) include:

- Bruising easily
- Prolonged bleeding from minor cuts
- The appearance of pinhead-sized red spots on the skin, called “petechiae”
- Frequent or severe nosebleeds
- Bleeding gums
- Heavier or more frequent menstrual periods in females

Other general symptoms of ALL include:

- Night sweats
- Pain in bones or joints
- Enlarged spleen, liver or lymph nodes
- Abdominal pain
- Pain or feeling of fullness below the ribs
- Unexplained weight loss or loss of appetite
- Wheezing, coughing or painful breathing

The symptoms of ALL may be like those of other blood disorders or medical conditions. Speak with your doctor if you have any of these symptoms to ensure proper diagnosis and treatment.

Diagnostic Testing

While certain signs and symptoms may indicate that a person has ALL, laboratory tests are needed to confirm the diagnosis. It is important to have an accurate diagnosis because it helps the doctor to:

- Estimate how the disease will progress
- Determine the appropriate treatment

Talk to your doctor about:

- The diagnostic tests that are being done
- What the results mean
- Getting copies of the test results

Some of these tests may be repeated both during and after treatment to evaluate the effectiveness of treatment.

Medical History. Your doctor will take a thorough medical history. The history may include information about past illnesses, injuries, treatments and medications. Some illnesses run in families, so the doctor may also ask about the health of your blood relatives.

Physical Examination. The doctor will want to know about your current symptoms and will conduct a physical examination. During the exam, the doctor may listen to your lungs and heart and carefully examine your body for signs of infection and disease. To check the internal organs, the doctor may also feel different parts of your body. For example, the doctor may feel the abdomen to see if you have an enlarged liver or spleen. Because ALL can cause enlarged lymph nodes, the doctor may check the lymph nodes in your neck, armpits and groin (top inner part of the thigh). In patients with testicles, the doctor may also examine the testicles to see if there are any lumps, swelling, or other signs of disease.

Complete Blood Count (CBC) with Differential. This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin in the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

People with ALL often have a high number of white blood cells, but most of these white blood cells are leukemia cells that do not protect against infection. Meanwhile, these patients do not have enough mature white blood cells and may also have a low number of red blood cells and platelets.

If the CBC test findings suggest leukemia, a diagnosis of ALL can sometimes be confirmed with additional testing of the blood sample. Sometimes, however, an ALL diagnosis can be made only after the examination of a sample of bone marrow cells. Less often, an ALL diagnosis is made after a biopsy of a lymph node mass. A lymph node biopsy is typically done to diagnose lymphoblastic lymphoma. Patients with enlarged lymph nodes may undergo both lymph node and bone marrow testing to correctly diagnose lymphoblastic lymphoma or lymphoblastic leukemia. For more information on lymph node biopsy, see page 10.

Bone Marrow Aspiration and Biopsy. Leukemia begins in the bone marrow. A diagnosis of ALL is confirmed by removing samples of bone marrow and examining them for leukemia cells. The procedures, called "bone marrow aspiration" and "bone marrow biopsy" are generally done at the doctor's office or in a hospital and both tests are usually done at the same visit.

After medicine has been given to numb the patient's skin and surface of the bone, the samples are usually taken through needles inserted into the back of the patient's hip bone. Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special, hollow needle is inserted through the back of the hip bone and into the bone marrow to aspirate (remove) a liquid sample of cells. For a bone marrow biopsy, a wider biopsy needle is used to remove a sample of solid bone that contains bone marrow. Both samples are sent to the lab where they are examined under a microscope. See **Figure 1** on page 9.

Figure 1. How are the Blood and Bone Marrow Tests Done?

Blood Test. Blood is taken from the patient's arm with a needle. The blood is collected in tubes and sent to a lab for testing.

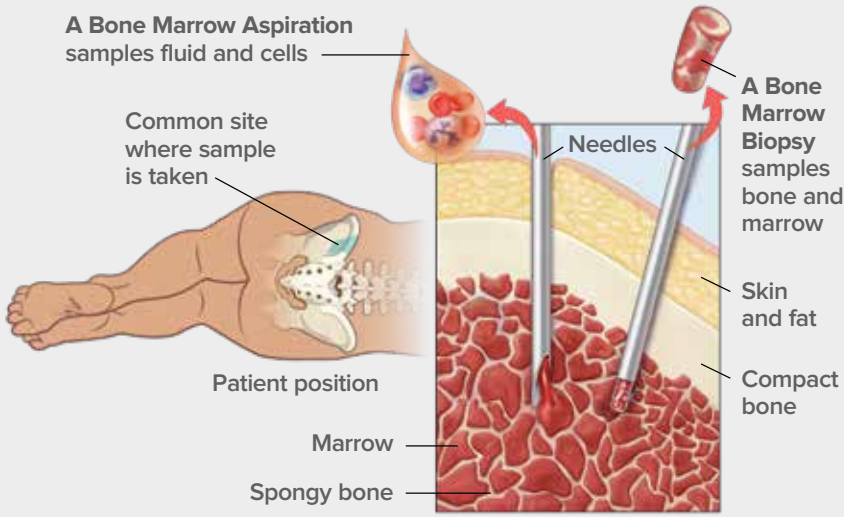
Bone Marrow Aspiration. A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

Bone Marrow Biopsy. A very small amount of bone filled with marrow cells is taken from the body and sent to a lab for testing.

Both bone marrow tests are done with special needles. Some patients are awake for the procedue. They get medication first to numb the part of the body that will be used to get the sample of cells. Some patients are given a drug that makes them sleep during this procedure. The sample of cells is usually taken from back of the patient's hip bone.

Blood and bone marrow tests may be done in the doctor's office or in a hospital. A bone marrow aspiration and biopsy are almost always done at the same visit. Blood and bone marrow tests may be done both during and after treatment. The tests are repeated to see if treatment is working.

Bone Marrow Aspiration and Biopsy



Left: The place on the back of the patient's hip bone where a bone marrow aspiration or biopsy is done. **Right:** Where the needle (on the left) goes inside the bone to collect the liquid sample for aspiration and the needle (on the right) to collect the bone sample for biopsy. The needles are different sizes for each of these tests.

Lymph Node Biopsy. A lymph node biopsy is a procedure in which all or part of a lymph node is removed and examined for signs of infection or disease such as cancer. Acute lymphoblastic lymphoma is diagnosed by removing all or part of an involved lymph node and examining the tissue under a microscope to look for cancer cells.

To ensure that there is enough tissue to make an accurate diagnosis, the preferred methods for the lymph node biopsy are often excisional or incisional. In an excisional biopsy, the whole lymph node is removed. In an incisional biopsy, only part of the lymph node is removed. If the lymph node is just under the skin, the biopsy procedure is usually simple and can sometimes be done with a local anesthetic (numbing medication). If the lymph node is deep inside the chest or abdomen (stomach area), the patient may be sedated or receive general anesthesia.

In certain situations, a "core needle biopsy" may be necessary if the lymph node is too difficult to reach. In this method, a wide needle is used to remove a column of tissue from the lymph node. This is done with local anesthesia to numb the area. Another type of needle biopsy, called fine-needle aspiration, is generally not suitable for diagnosing lymphoma. This is because the long, thin needle that is used to draw out fluid and cells often does not collect enough cells to make an accurate diagnosis.

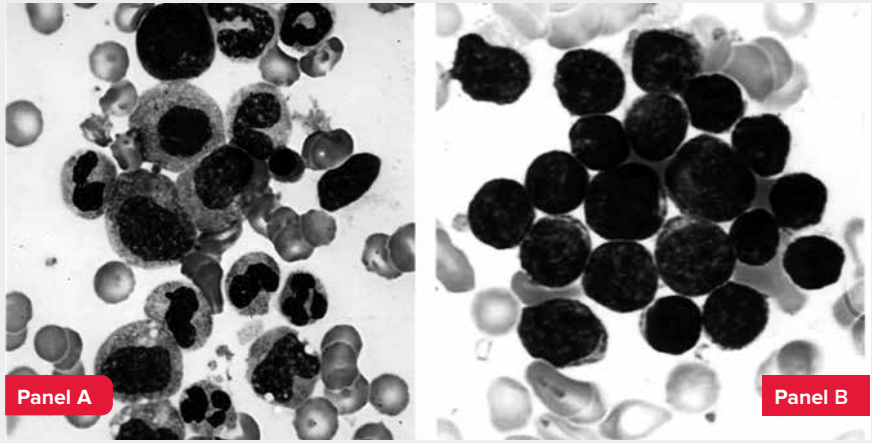
Cell Assessment. At the laboratory, a doctor called a "hematopathologist" examines the blood and bone marrow samples and, if taken, the lymph node biopsy samples. A hematopathologist is a doctor who has special training in identifying blood diseases by studying cells under a microscope.

The hematopathologist examines the samples to determine their size, shape and type, and to identify other cell features. Whether the cells look like normal, mature blood cells or abnormal, immature blood cells (blast cells) is an important finding. See **Figure 2** on page 11.

The percentage of blast cells identified in the samples is another important finding. Typically, there are no blast cells in the blood, and no more than 5 percent of the cells in the bone marrow are blast cells.

A diagnosis of ALL generally requires that at least 20 percent of the cells in the bone marrow are blasts. In most people diagnosed with ALL, the level of blast cells in the bone marrow is well over 20 percent, but a higher percentage of blast cells in the bone marrow does not necessarily indicate a poorer prognosis.

Figure 2. Acute Lymphoblastic Leukemia (ALL) Cells



Panel A shows a photograph of developing cells in healthy marrow. The variation in the appearance of the cells is characteristic of normal marrow. **Panel B** shows a photograph of marrow cells from a patient with acute lymphoblastic leukemia. An unvaried appearance characterizes the leukemic blast cells.

If leukemia is found, additional tests are done on the biopsy samples to gather information about the subtype of ALL.

Immunophenotyping (Flow Cytometry). This lab test identifies the antigens, or proteins, on the surface of cancer cells. Finding (or not finding) certain proteins can help the hematopathologist determine the type of leukemia or lymphoma. The pattern of the surface proteins is called the "immunophenotype." A bone marrow sample is often used for this test, but it can also be done using cells from the blood, lymph nodes and other tissues.

Immunophenotyping is done with an instrument called a "flow cytometer." A flow cytometry test can measure the number of cells in a sample, as well as specific characteristics of the cells including their size and shape, and identify specific markers on the cell surfaces. A sample of cells is tagged with a panel of antibodies that are specific to areas on the cell surfaces. The cells are stained with a light-sensitive dye and are passed through a laser beam in the flow cytometer. If they have an antibody-specific surface marker, the cells light up and are counted.

Leukemia cells can have different antigens (proteins) on their surfaces, depending on the type of leukemia. Finding, or not finding, these antigens, called "cluster of differentiation (CD) proteins," can help the hematopathologist determine the type of leukemia.

Flow cytometry is used to determine the type of lymphocytes (B cells or T cells) and to assess the maturity of the cells. B-cell ALL and T-cell ALL each have a common pattern of proteins.

B-cell ALL lymphoblasts typically express CD10, CD19, CD22 and CD79a on their surface. CD20 may also be expressed in approximately 50 percent of B cells in adults with ALL. Alternatively, T-cell ALL cells commonly express CD1a, CD2, CD3, CD5 and CD7.

In addition to diagnosis, flow cytometry is also used after treatment for evaluating minimal/measurable residual disease (MRD). This refers to the small number of cancer cells that may remain in the body after treatment (for more information on MRD, see page 33).

Genetic Tests. Cancer is a disease caused by mutations (changes) to the genetic material inside of cells. This genetic material is called DNA (deoxyribonucleic acid). Inside cells, DNA is packaged into thread-like structures called "chromosomes." Each person's cancer has a unique combination of genetic mutations. Except in very rare cases, these mutations develop during the course of one's life. That means you were not likely born with these mutations, nor is it likely that they can be "passed down" to your children.

Genetic testing should be done when the cancer is first diagnosed and may also be indicated after a relapse. This is because it is possible for patients to acquire additional genetic abnormalities after the completion of their initial, "first-line" treatment.

The following tests are used to examine the chromosomes and genes in the leukemia cells.

Cytogenetic Analysis (Karyotyping). In this test, a hematopathologist or other type of specialist uses a microscope to examine the chromosomes inside cells. In patients with ALL, cytogenetic analysis is used to look for abnormal changes in the chromosomes of leukemia cells.

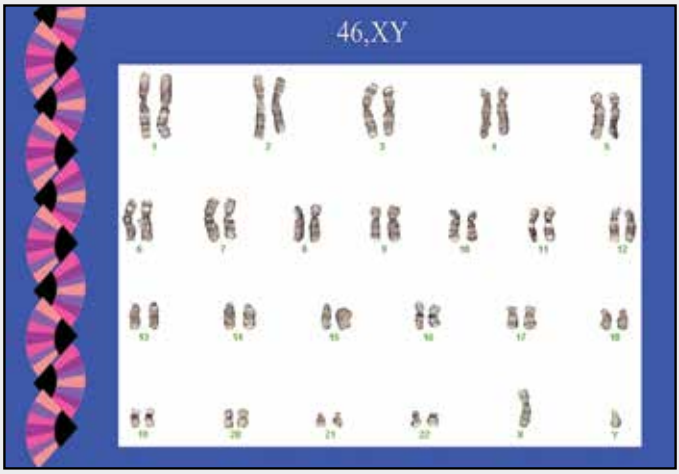
Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure. In many cases of ALL, the chromosomes of leukemia cells have abnormal changes that can be seen under a microscope.

The leukemia cells in the sample are allowed to grow in the laboratory and then are stained prior to examination. The stained sample is examined under a microscope and photographed to show the arrangement of the chromosomes, called a "karyotype." The karyotype shows if there are any abnormal changes in the size, shape, structure or number of chromosomes in the leukemia cells. See **Figure 3** on page 13.

Cytogenetic analysis provides information for determining a patient's prognosis (the likely outcome of the disease) and treatment options. This information can predict how the disease will respond to treatment. For example, a translocation between chromosomes 9 and 22 is associated with a diagnosis of Philadelphia

chromosome-positive (Ph+) ALL, a subtype of ALL treated differently from other subtypes. A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. See page 36 for more information on Ph+ ALL.

Figure 3. Normal Male Karyotype



This figure shows a normal male karyotype. Courtesy of Dr. Dong Chen, hematopathologist, Mayo Clinic, Rochester, MN.

Fluorescence in Situ Hybridization (FISH). This very sensitive test is used to examine genes or chromosomes in cells and tissues. Doctors use FISH to detect certain abnormal changes in the chromosomes and genes of leukemia cells. Pieces of DNA that contain special fluorescent dyes are prepared in the laboratory and added to the leukemia cells on a glass slide. The pieces of DNA that bind to certain genes or areas of chromosomes light up when the slide is viewed under a specialized "fluorescence" microscope. Not only can FISH identify most abnormal changes that can be seen with a microscope, but it can also detect some changes that are too small to be seen with basic cytogenetic testing. However, FISH is not used as a general screening tool, and this test has one disadvantage—the doctor must select the specific chromosomes or genes to examine before the test is performed.

Polymerase Chain Reaction (PCR). This is a very sensitive lab test used to detect and measure certain genetic mutations and chromosomal changes that are too small to be seen with a microscope. PCR essentially increases or "amplifies" small amounts of specific pieces of either RNA (ribonucleic acid) or DNA (deoxyribonucleic acid) to make them easier to detect and measure. This test can find a single leukemia cell among more than 100,000 normal cells. PCR testing is one method used to determine the amount of minimal/measurable residual disease (MRD) in patients, which refers to the small amount of cancer cells that may remain in the body after treatment. This test can be done with either a bone marrow sample or a blood sample.

Next-generation sequencing. This technique refers to several different laboratory tests that can rapidly examine the exact sequence (order) of the genetic code in DNA or RNA. This makes it possible to identify a variety of genetic alterations in a patient's cancer cells. These alterations are important in guiding risk assessment and prognosis and may also guide treatment decisions. Next-generation sequencing may help determine which patients are at high risk and may need more intensive treatment or who may benefit from treatment with novel therapies. The number of mutated genes that can be detected in ALL patients has increased considerably with the availability of next-generation sequencing.

There are also ways to use this technique to look for MRD after treatment, by identifying and tracking some of these unique sequences of genetic code that serve as a marker for ALL cells. This method is extremely sensitive, as it can find a leukemia cell among as many as 1,000,000 normal cells.

See the free LLS books *Understanding Genetics* and *Understanding Lab and Imaging Tests* for more information about these tests.

Visit www.LLS.org/3D to view interactive 3D illustrations of some lab and imaging tests.

Diagnosis and Cell Classification

The diagnosis of ALL generally requires 20 percent or more of the cells in the bone marrow to be lymphoblasts. The ALL subtype is determined based on the patient's lab test results.

Subtypes of ALL. The subtypes of ALL are based on certain features of the leukemia cells. Determination of the ALL subtype is an important factor in treatment planning. Based on a patient's ALL subtype, the doctor will decide which drugs, drug combinations and drug dosages are indicated, and will determine the appropriate duration of treatment.

Immunophenotyping. Leukemia cells can be classified by antigens found on their surfaces, known as "immunophenotypes." The World Health Organization (WHO) classifies ALL based on the immunophenotype of the leukemia cell in the following ways (see **Table 1** on page 16):

- B-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into B cells. If the bone marrow has 20 percent or more lymphoblasts, the disease is called B-cell lymphoblastic leukemia (B-cell ALL). If the lymphoblasts are restricted to a mass in a lymph node or other lymph tissue and less than 20 percent of the bone marrow cells are lymphoblasts, it is called B-cell lymphoblastic lymphoma. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy.

  B-cell ALL is the most common ALL subtype, accounting for 75 percent of adult cases of ALL. Within the B-cell lineage, the cell surface markers (proteins) differ according to the stage of cell maturation.

  Before 2008, the WHO classified B-cell lymphoblastic leukemia as "precursor B-lymphoblastic leukemia." This older term is sometimes used to distinguish it from mature B-cell ALL. Mature B-cell ALL is now referred to as "Burkitt leukemia." The treatment for Burkitt leukemia is unique in that it can resemble treatment used for both ALL and Burkitt lymphoma, a type of non-Hodgkin lymphoma. **For more information on Burkitt lymphoma, see the free LLS booklet *Non-Hodgkin Lymphoma*.**

- T-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into T cells. If 20 percent or more of the bone marrow T cells are lymphoblasts, the disease is called T-cell lymphoblastic leukemia (T-cell ALL). If the lymphoblasts are restricted to a mass in a lymph node or other lymph tissue and less than 20 percent of the bone marrow cells are lymphoblasts, it is called T-cell lymphoblastic lymphoma.

  T-cell ALL is less common than B-cell ALL, accounting for about 25 percent of adult ALL cases.

Table 1. World Health Organization Classification of Acute Lymphoblastic Leukemia (ALL)

B-cell lymphoblastic leukemia/lymphoma

- B-cell lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)
- B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- B-cell lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
- B-cell lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
- B-cell lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
- B-cell lymphoblastic leukemia/lymphoma with hyperdiploidy
- B-cell lymphoblastic leukemia/lymphoma with hypodiploidy
- B-cell lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
- B-cell lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
- *Provisional entity: B-cell lymphoblastic leukemia/lymphoma, BCR-ABL1–like*
- *Provisional entity: B-cell lymphoblastic leukemia/lymphoma with iAMP21*

T-cell lymphoblastic leukemia/lymphoma

Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Source: Classification of Acute Lymphoblastic Leukemia Types, created by the World Health Organization (WHO).

Genetic Changes. In addition to classifying ALL as either B-cell or T-cell ALL, it is further classified based on certain changes to the chromosomes and genes found in the leukemia cells (see **Table 2** below). This identification of specific genetic abnormalities is critical for disease evaluation, risk stratification and treatment planning.

Translocations are the most common type of genetic change associated with ALL. In a translocation, the DNA from one chromosome breaks off and becomes attached to a different chromosome. Sometimes pieces from two different chromosomes trade places. A translocation may result in a "fusion gene," an abnormal gene that is formed when two different genes are fused together.

Another type of genetic change that occurs in ALL is the result of numerical abnormalities. A numerical abnormality is either a gain or loss in the number of chromosomes from the normal 46 chromosomes. A change in the number of chromosomes can affect the growth, development and functioning of body systems.

About 75 percent of adult ALL cases can be classified into subgroups based on chromosomal abnormalities and genetic mutations. Not all patients have the same genetic changes. Some changes are more common than others, and some have a greater effect on a patient's prognosis.

See the free LLS booklet *Understanding Genetics* for more information about genetics and genetic testing.

Table 2. Common Chromosomal and Molecular Abnormalities in ALL

Cytogenetics	Gene(s) Associated	Frequency in Adults
Hyperdiploidy (>50 chromosomes)	—	7%
Hypodiploidy (<44 chromosomes)	—	2%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	*BCR-ABL1*	25%
t(12;21)(p13;q22)	*ETV6-RUNX1 (TEL-AML1)*	2%
t(v;11q23) [eg, t(4;11) and others], t(11;19)	*KMT2A rearranged*	10%
t(1;19)(q23;p13)	*TCF3-PBX1 (E2A-PBX1)*	3%
t(5;14)(q31;q32)	*IL3-IGH*	< 1%
t(8;14), t(2;8), t(8;22)	*c-MYC*	4%
t(1;14)(p32;q11)	*TAL-1*[a]	12%

Table 2. (Continued)

Cytogenetics	Gene(s) Associated	Frequency in Adults
t(10;14)(q24;q11)	*HOX11 (TLX1)*	8%
t(5;14)(q35;q32)	*HOX11L2*[a]	1%
t(11;14)(q11)[eg, (p13;q11), (p15;q11)]	*TCRα* and *TCRσ*	20-25%
BCR-ABL1-like/Ph-like	various	10-30%
B-ALL with *iAMP21*	*RUNX1*	—
ETP	various	2%
Ikaros	*IKZF1*	25-35%

[a]Abnormalities observed exclusively in T-cell ALL; all others occur exclusively or predominantly in B-cell ALL.

Abbreviations: t, a translocation between chromosomes; q, the long arm of a chromosome (the lower half); p, the short arm of a chromosome (the upper half).

Adapted from NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. 2022.

Treatment Planning

Choosing a Hospital and Doctor. A diagnosis of ALL is associated with a wide range of outcomes, so it is essential to seek treatment in a center with hematologist-oncologists who are experienced in the care of patients who have ALL. A hematologist is a doctor who has special training in disorders of the blood, and an oncologist is a doctor who has special training in cancer. Doctors with training in both hematology and oncology have particular expertise in treating blood cancers.

Typically, ALL patients need to start treatment as soon as possible after diagnosis. If time allows, however, you may want to seek a second opinion from another doctor. A second opinion may help you feel more confident about the recommended treatment plan. The second opinion should come from another hematologist-oncologist, preferably one who treats ALL. This doctor will usually have the most knowledge and experience about the latest treatment options.

If you are unsure or feel uncomfortable about how to tell your doctor you are getting a second opinion, call an LLS Information Specialist to discuss a way that makes you feel comfortable. You may also want to check with your health insurance company to be sure that your policy covers the cost of getting a second opinion.

Fertility. Some cancer treatments can affect fertility (the ability to have children in the future). Changes to fertility, which can happen to both men and women, may be temporary or permanent. Before you begin your cancer treatment, it is important to talk with your doctor about whether your treatment could affect your fertility.

For those who want to have children in the future, you may want to speak with a fertility specialist. A fertility specialist is a doctor who diagnoses and treats problems related to infertility. The fertility specialist can talk to you about possible options for preserving your fertility. You may be able to take steps before treatment begins to preserve your fertility. However, delaying treatment to address fertility options may not always be recommended. You may need to start treatment right away.

For more information about fertility preservation, see the free LLS booklet *Fertility and Cancer*.

Pre-Treatment Testing. Before you start treatment, your doctor will perform tests to learn more about your leukemia and overall health and to find out if your leukemia has spread to other parts of your body. Doctors use this information for treatment planning. Some of these tests are summarized below.

Blood Tests. The following are blood tests used for treatment planning:

Complete Blood Count (CBC) with Differential. This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin in red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

Blood Chemistry Profile. This blood test measures the levels of certain substances released into the blood by organs and tissues in the body. These substances include electrolytes (such as sodium, potassium and chloride), fats, proteins, glucose (blood sugar), uric acid and enzymes. Blood chemistry test findings indicate how well a person's kidneys, liver and other organs are working. A blood chemistry profile also provides helpful information about any potential organ damage caused by leukemia cells or cancer treatments.

Liver Function Tests. The liver is the largest organ inside the body. It is in the upper right side of the abdomen. It helps the body digest food, store energy and remove toxins from the blood. If leukemia cells are present in the liver, they can affect liver function. Some chemotherapy drugs can also damage the liver, which can also affect liver function. Liver function tests are done to check how well the liver is working.

Coagulation Tests. These tests measure the blood's ability to clot and stop injuries from bleeding. Certain proteins, called "coagulation factors," are needed for clotting. Most of these proteins are made by the liver. In addition to checking how well the blood can clot, these tests can determine whether there are deficiencies in some proteins, such as one called fibrinogen, a protein that helps blood clot. A coagulation test can help the doctor determine if your blood is clotting properly. This is important because ALL itself can sometimes affect blood clotting, and later, so can treatment for ALL. If the clotting system is not working normally, it can lead to serious complications like bleeding or the abnormal formation of blood clots.

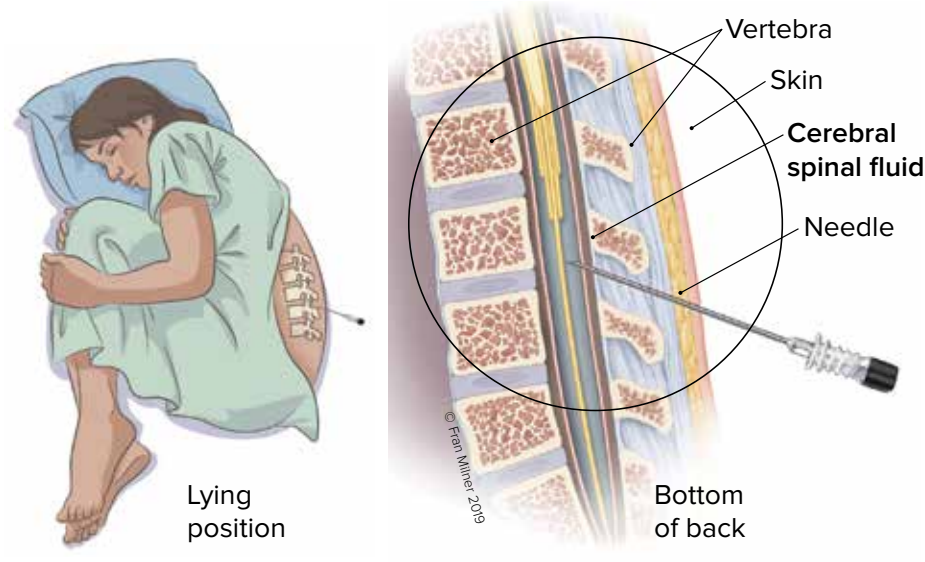
Tumor Lysis Syndrome (TLS Panel). Patients with ALL may be at high risk for developing a condition called "tumor lysis syndrome" (TLS). This condition can occur when a large number of cancer cells die within a short period of time. As the leukemia cells die, they break apart and release their contents into the bloodstream, which changes the normal balance of chemicals in the blood. This can overwhelm the kidneys because they cannot get rid of these substances all at once. The effects of TLS can be life-threatening; they can be severe at the time of initial leukemia diagnosis and during the early phases of treatment, especially if white blood cell counts are very high before beginning therapy. A TLS panel can help your doctor assess if you are likely to get TLS or if you already have it.

HLA Typing. This consists of a blood test to identify certain proteins, called human leukocyte antigens (HLAs), found on the surface of most cells in the body. These proteins make up a person's tissue type, which varies from person to person. They also play an important role in the body's immune response to foreign substances by helping the body distinguish its own cells from foreign cells. HLA typing is done before allogeneic stem cell transplantation to find out if there is a tissue match between the donor and the patient. It is an important test for newly diagnosed ALL patients if allogeneic stem cell transplantation is being considered as a treatment option. For more information on stem cell transplantation, see page 29.

Lumbar Puncture. ALL can spread to the cerebrospinal fluid, the fluid that flows around the brain and spinal cord. To determine whether leukemia cells have spread to this area, a sample of the cerebrospinal fluid is tested.

After the area over the spine in the lower part of the back has been numbed with a local anesthetic, a thin needle is inserted between two vertebrae (bones that form the spinal column) and into the cerebrospinal fluid. See **Figure 4** on page 21. A sample of the fluid is withdrawn and examined under a microscope to look for leukemia cells that may have spread to the brain and spinal cord.

Figure 4. Lumbar Puncture



Imaging Tests. These tests create images (pictures) of the inside of the body. A radiologist is a doctor who specializes in reading these images. Various types of imaging tests are used to detect where cancer is located in the body.

Computed Tomography (CT) Scan. In this type of imaging test, a computer linked to an x-ray machine is used to take a series of detailed pictures of areas inside the body. In some cases, leukemia may grow outside the bone marrow—most commonly in lymph nodes. A CT scan may be used to see whether leukemia cells are accumulating in lymph nodes in the chest or abdomen, or in organs such as the spleen and liver.

Positron Emission Tomography (PET) Scan. For this type of imaging test, a small amount of radioactive glucose (sugar) is injected into a patient's vein. The PET scanner detects areas in the body where large amounts of glucose are being used. In the images, the cancer cells appear brighter than the normal cells because they use glucose more quickly than normal cells. A PET scan may be done to see if there are cancer cells in the lymph nodes or organs.

Positron Emission Tomography-Computed Tomography (PET-CT) Scan. This procedure combines images from both a PET scan and a CT scan. The combined scans give a more detailed image of areas inside the body than either scan can by itself. If lymphoblastic lymphoma is suspected, a "whole-body" PET/CT scan is recommended.

Magnetic Resonance Imaging (MRI) Scan. This imaging test uses magnetic fields and radio waves to create images of the body's organs and tissues, as well as the brain and spinal cord. An MRI scan of the head and/or spinal cord should be done

if a patient has symptoms such as headaches or seizures that suggest that ALL cells may have spread to the brain and spinal cord.

Ultrasound. This imaging test uses high-energy sound waves to examine tissues and organs inside the body. For example, it can detect cancer in the testicles of males. If the testicles are not the same size or have any lumps, the doctor may order an ultrasound to see whether there is a mass in the testicles.

Echocardiogram. A computerized image of the heart is created by bouncing ultrasound waves off internal tissues or organs in the chest. An echocardiogram shows the size, shape and position of the heart, as well as its internal structures. It also shows if the heart is beating and pumping blood normally. Because some cancer treatments can damage the heart, the doctor may do this test as part of the treatment planning process to check how well the heart can pump blood.

See the free LLS booklet *Understanding Lab and Imaging Tests* for more information about these tests. To view interactive 3D illustrations of some lab and imaging tests, visit www.LLS.org/3D.

Prognostic Factors. Certain factors can affect a patient's prognosis—the probable outcome of this patient's cancer. These are called "prognostic factors." Doctors use prognostic factors to help predict how a patient's disease is likely to respond to treatment. These factors help doctors plan the most appropriate initial treatment regimen for each patient. In addition, they help determine whether stem cell transplantation should be considered as a treatment option for the patient, and if so, when to perform the transplant.

The prognostic factors for adults with ALL are summarized below.

- Age: Younger adults have a better prognosis. The leukemia cells in older patients tend to be more resistant to treatment. Patients older than 35 years have decreased remission duration and a harder time tolerating chemotherapy.
- White blood cell count: Patients with a lower white blood cell count (less than 30,000/µL for B-cell ALL and less than 100,000/µL for T-cell ALL) at the time of diagnosis generally have a better prognosis.
- Gene or chromosome abnormalities: Certain changes in the chromosomes or genes of leukemia cells can make the disease either easier or harder to treat. See **Table 3** on page 23 for risk groups for adults with B-cell ALL.
- Presence of central nervous system (CNS) disease: Patients with ALL who have leukemia cells in the central nervous system at diagnosis are at a higher risk of disease relapse.
- Response to induction therapy: Patients who have a better response to their initial therapy, called "induction therapy," typically have a better outcome.

Table 3. Cytogenetic Risk Groups for B-Cell ALL

Risk Groups	Cytogenetics
Good risk	• Hyperdiploidy (51-65 chromosomes) ◦ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): *ETV6-RUNX1*

Poor risk	• Hypodiploidy (<44 chromosomes)
	• *KMT2A* rearranged (t[4;11] or others)
	• t(v;14q32)/IgH
	• t(9;22)(q34;q11.2): *BCR-ABL1* (defined as "high risk" in the pre-TKI era)
	• Complex karyotype (5 or more chromosomal abnormalities)
	• *BCR-ABL1*-like (Ph-like) ALL
	  ◦ JAK-STAT (*CFLF2r*, *EPORr*, *JAK1/2/3r*, *TYK2r*, mutations of *SH2B3*, *IL7R*, *JAK1/2/3*)
	  ◦ ABL class (rearrangements of *ABL1*, *ABL2*, *PDGFRA*, *PDGFRB*, *FGFR*)
	  ◦ Other (*NTRKr*, *FLT3r*, *LYNr*, *PTK2Br*)
	• Intrachromosomal amplification of chromosome 21 (iAMP21)
	• T(17;19): *TCF3-HLF* fusion
	• Alterations of *IKZF1*

Abbreviations: ALL, acute lymphoblastic leukemia; Ph-like, Philadelphia-like; TKI, tyrosine kinase iinhibitor; t, a translocation between chromosomes; q, the long arm of a chromosome (the lower half); p, the short arm of a chromosome (the upper half).
Source: The National Comprehensive Cancer Network (NCCN) Acute Lymphoblastic Leukemia Guidelines. 2022.

Treatment Options Overview

New treatments may have been approved since this book was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you.

Talk to your doctor about:

- ○ Your treatment options and the results you can expect from treatment
- ○ The possibility of participating in a clinical trial

Administration of Therapies. Treatments are given in different ways, including:

- Intravenous treatment. During an intravenous (IV) infusion, the drugs are injected slowly into a vein over the course of several minutes, a few hours, or even several days (in the case of a continuous infusion). Often, doctors give IV treatment through a thin, soft tube called a central venous line (also called a central line or catheter), which is placed in a large blood vessel in the neck, chest or arm. When a patient has a central line in place, the drugs are given through the line, and doctors do not have to inject a needle into the patient's vein each time a treatment is administered. Doctors can also use the central line to give other medications and take blood samples. A central line can be left in place for weeks or months but must be carefully cleaned and maintained to minimize the risk of infections entering the bloodstream.
- Intramuscular injection. This treatment uses a needle to put medicine deep into the muscle. Patients may get an intramuscular injection in an arm or a leg.
- Oral treatment. Oral medications are taken by mouth and come in a variety of forms, including pills, capsules and liquids. It is important to always follow directions carefully for oral medications, including the need for special handling (gloves), storage (room temperature or refrigerated) and disposal. Keeping a diary to track oral medication may be helpful.
- Intrathecal treatment. This is treatment in which medicine is injected in the fluid-filled space that surrounds the brain and spinal cord, called the cerebrospinal fluid, typically via a lumbar puncture (see **Figure 4** on page 21). This method of treatment is most commonly used to prevent the leukemia cells from entering this space, but it is also employed if there are signs that leukemia cells have already spread to the brain or spinal cord. See *Central Nervous System (CNS) Prophylaxis and Treatment* on page 32.
- Subcutaneous injection. With subcutaneous injection, the needle goes under the skin into the space between the skin and muscle, but it does not enter the muscle.

Types of Treatment. Not everyone with ALL receives the same type of treatment. Your doctor will tailor your treatment based on your ALL subtype and other factors such as your age, overall health and your response to treatment. Your treatment may include chemotherapy, targeted therapy, stem cell transplantation, immunotherapy, and/or a treatment called "CAR T-cell therapy."

Chemotherapy. The current standard treatment for ALL is long-term chemotherapy. It typically lasts for about 2 to 3 years, and it is often intense, especially in the first few months of treatment. The most common treatment regimens use a combination of more than one anti-cancer drug.

Chemotherapy drugs kill fast-growing cells throughout the body, including both cancer cells and normal, healthy cells. Different types of chemotherapy drugs work in different ways to kill leukemia cells or to stop new leukemia cells from forming. As a result, more than one chemotherapy drug is usually used.

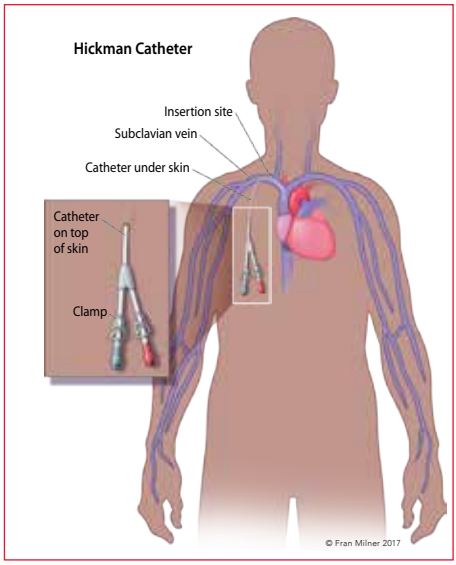
Chemotherapy is typically given in cycles. Each cycle is made up of a number of days of treatment, followed by a certain number of days of rest. The rest days allow the body time to recover before the next treatment cycle begins. Cycles vary in length, depending on which drugs are used.

Some chemotherapy drugs are injected into a vein using a "catheter." A catheter is a thin, flexible tube that is used to give chemotherapy and other drugs, blood transfusions and fluids directly into the patient's bloodstream. It can also be used to remove blood for testing.

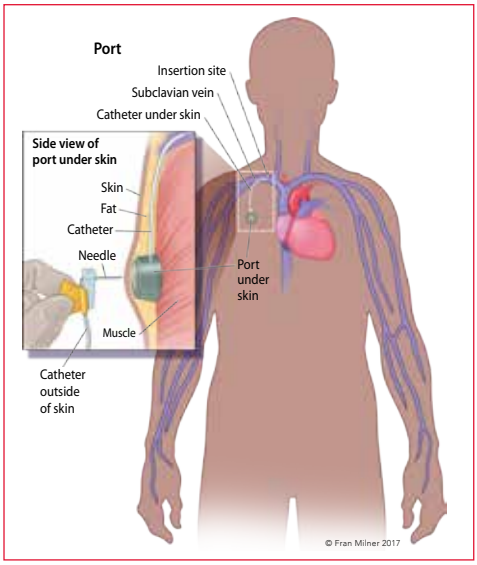
Types of catheters include:

- Hickman Catheter. This type of catheter is a thin, flexible tube that is inserted into a vein in the chest. It is threaded under the skin into a larger vein above the right side of the heart called the superior vena cava. Part of the catheter remains outside the body. It is taped to the chest and is used to give chemotherapy, so the patient does not have to endure "needle sticks." See **Figure 5** on page 26 (the illustration on the left).
- Port. A port is a small, round disc that is usually placed under the skin in the chest during surgery. This is usually done with local anesthesia or with a patient under conscious sedation. The port is connected by a catheter to a large vein in the chest. Chemotherapy is given through a needle that is inserted through the skin into the port. The needle is removed after the drugs are given. This type of catheter is completely inside the body. See **Figure 5** on page 26 (the illustration on the right).
- Peripherally inserted central catheter (PICC). This is similar in appearance and function to the Hickman catheter. However, it is placed in one of the larger veins in the upper arm (that is, peripherally) instead of in the chest. One of the benefits of this device is that it can be placed relatively quickly.

Figure 5. Methods of Intravenous (IV) Injection: Hickman® Catheter and Port



Hickman® Catheter: An example of a type of central line.



Port: A port used with a central line.

Radiation Therapy. Radiation therapy, also known as "radiotherapy," uses high-energy x-rays or other types of radiation to kill cancer cells in a small, targeted area of the body. Because radiation can also harm normal cells, whenever possible, radiation therapy is directed only at the areas that are affected with cancer, in order to reduce the long-term side effects.

Radiation therapy may be used to treat ALL that has spread to the central nervous system (brain and spinal cord) or testicles. It may also be used to prepare the bone marrow for a stem cell transplantation.

Targeted Therapy. Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells, with less harm to normal cells. Not all cancers have the same targets. Each type of targeted therapy works a little bit differently, but they all interfere with the growth and survival of cancer cells. To find the most effective treatment, your doctor may run tests to identify the genes, proteins and other factors in your cancer cells. This helps the doctor choose the most effective treatment for you, based on the specific factors of your disease. Targeted therapy may be used alone or in combination with chemotherapy. Some types of targeted therapy include:

Tyrosine Kinase Inhibitors (TKIs). Tyrosine kinases are enzymes that are a part of many cell functions including cell signaling, growth and division. These enzymes may become too active in patients with an ALL subtype called Philadelphia chromosome-positive ALL (Ph+ ALL). For more information on Ph+ ALL, see page 36.

TKIs work to block these overactive enzymes and may stop cancer cells from growing. TKIs are pills taken by mouth. They are generally not used alone to treat ALL. Instead, they are added to other medications, such as a combination chemotherapy regimen. TKIs used in the treatment of Ph+ ALL include **imatinib (Gleevec®)**, **dasatinib (Sprycel®)**, **ponatinib (Iclusig®)**, **bosutinib (Bosulif®)**, and **nilotinib (Tasigna®)**. For more information about these drugs, see page 53.

Common side effects of TKIs include low blood counts, abnormal bleeding, pain, nausea and vomiting, diarrhea, fatigue, rashes, headaches, and pain in muscles, bones and joints. TKIs may also cause fluid to collect under the eyes, and in the hands, feet or lungs. Uncommon but serious side effects include a change in the rhythm of the heart, inflammation of the pancreas, blood vessel narrowing or blood clot formation.

Another 10 to 30 percent of adults who have ALL have a subtype known as “Philadelphia chromosome-like ALL” (Ph-like ALL). Unlike those with Ph+ ALL, who share a similar genetic mutation, patients with Ph-like ALL have a highly diverse range of genetic mutations that activate tyrosine kinase signaling. Researchers are working to understand better ways to identify these genetic mutations to determine whether specific TKIs may be effective.

Immunotherapy. Immunotherapy treatments use substances that can stimulate and/or suppress the immune system to help the body fight cancer. There are immunotherapy treatments that target proteins, called cluster of differentiation (CD) antigens, on the surface of leukemia cells. B-cell ALL is typically characterized by the presence of the proteins CD10, CD19, CD20, CD22, CD24 and CD79a. T-cell ALL is typically associated with the presence of CD3.

Monoclonal Antibodies. Monoclonal antibodies are proteins that are made in a laboratory. They can bind to substances in the body, including cancer cells. Most are designed to attach to one specific substance. These drugs can be used alone to destroy cancer cells, or to carry drugs, toxins, or radioactive substances directly to the cancer cells.

- **Blinatumomab (Blincyto®)** is a "bispecific" antibody, a type of antibody that can bind to two different antigens at the same time. Blinatumomab is a liquid administered slowly into a vein by IV as a continuous infusion over a period of 28 days. Hospitalization of the patient is typically recommended for the first few days of treatment. Side effects of blinatumomab may include fever, headache, infection, nausea, diarrhea and neurological complications such as seizures, confusion, slurred speech and loss of balance.

- **Inotuzumab ozogamicin (Besponsa®)** is a monoclonal antibody linked to a chemotherapy drug that is indicated for the treatment of patients with relapsed or refractory B-cell ALL. Inotuzumab ozogamicin targets CD22, a surface protein expressed on the cancer cells of most B-cell ALL patients. When inotuzumab ozogamicin binds to the CD22 antigen on a B cell, it enters the cell and then releases the chemotherapy drug **calicheamicin,** causing the cell to die.

  Inotuzumab ozogamicin is administered by IV infusion and, for appropriate patients, can be given in an outpatient setting. Common side effects include increased risk of infection, bleeding, fatigue, fever, nausea, headache and abdominal pain. Liver injury is also seen and, in rare instances, can be serious and even fatal. Older patients, as well as patients with pre-existing liver disease and those who undergo stem cell transplantation, appear to be at greater risk of serious forms of liver toxicity.

- **Rituximab (Rituxan®)** is a monoclonal antibody that binds to CD20, a protein found on the surface of healthy B cells and on the lymphoblastic B cells of approximately 50 percent of adults with B-cell ALL. When rituximab binds to CD20, it signals the cell to die. Rituximab is not used alone to treat ALL; it is added to a chemotherapy regimen. Some studies have shown that the addition of rituximab to standard chemotherapy improved survival among adults with CD20-positive ALL. Side effects may include allergic reactions, infections, chills, fatigue, body aches and low blood cell counts.

See *Some Drugs Used in the Treatment of ALL* starting on page 50.

Chimeric Antigen Receptor (CAR) T-Cell Therapy. CAR T-cell therapy is a type of immunotherapy that consists of engineering a patient's own immune cells called T cells (white blood cells that help the body fight infections and cancer) to first recognize and then attack cancer cells. Each dose of CAR T-cell therapy is made for a specific patient. The T cells are collected from the patient and then genetically modified in a laboratory to add new genes called "chimeric antigen receptors" (CARs). These receptors recognize and bind to a specific target found on the leukemia cells. The most frequently targeted antigen in CAR T-cell therapy for leukemia is called "cluster of differentiation 19" (CD19). The CD19 antigen is expressed on the surface of nearly all healthy and cancerous B cells, including ALL cells. The genetically modified CAR T cells are infused back into the patient's body to find and kill leukemia cells with CD19 on their surfaces.

This type of treatment is often recommended for high-risk patients: for example, those who relapse after stem cell transplantation or when stem cell transplantation is not a treatment option. While this treatment can be very effective, it is also associated with a relatively high rate of serious complications and is usually only recommended for physically fit patients. As a result, it can be given only at specialized cancer centers that have expertise in delivering this form of treatment.

There are two FDA-approved CAR T-cell treatments approved for adults with ALL:

- **Brexucabtagene autoleucel (Tecartus®)**.
- **Tisagenlecleucel (Kymriah®)**.

See *Some Drugs Used in the Treatment of ALL* starting on page 50.

For more comprehensive information, see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts.* Visit www.LLS.org/TreatmentVideos for videos about CAR T-cell therapy.

Stem Cell Transplantation. Some patients with ALL may benefit from stem cell transplantation. The goal of stem cell transplantation is to cure the patient's cancer by destroying cancer cells in the bone marrow with high doses chemotherapy, with or without radiation therapy. However, these treatments can cause very serious side effects. Although administering high-dose therapy like this can kill more leukemia cells, it can also severely damage the stem cells in the bone marrow and may result in anemia, serious infections and uncontrolled bleeding. After this treatment, the patient receives an infusion of healthy stem cells to replace those that were destroyed. The healthy blood stem cells grow and multiply, forming new bone marrow and blood cells.

There are two main types of stem cell transplantation:

- Allogeneic—A patient receives stem cells from a matched or a partially matched donor, either related or unrelated to the patient.
- Autologous—A patient's own stem cells are collected, stored and then given back to the patient after completing a course of chemotherapy.

Stem cell transplantation is not used as the first or the primary treatment for ALL. It may be part of the treatment plan for high-risk ALL patients, or for patients who do not respond to other treatments.

Stem cell transplantation is a complex treatment. It can cause serious side effects that can be life-threatening, so it may not be a treatment option for every ALL patient. The decision to undergo a transplant should be discussed with your doctor. Your doctor will consider many factors, including your age, general health, certain prognostic factors, previous treatments, and if you have a well-matched donor.

Allogeneic Stem Cell Transplantation. This is the most common type of stem cell transplantation used to treat ALL. In preparation for the transplant, patients are given high doses of chemotherapy, either with or without radiation therapy, to kill the remaining leukemia cells still present in the body. This part of the treatment, called "myeloablative conditioning," also kills cells in the bone marrow, including normal blood-forming cells. After the high-dose chemotherapy is completed, patients receive an infusion of the donor stem cells. The donated stem cells restore the bone marrow's ability to form new blood cells.

An allogeneic stem cell transplantation creates a new immune system for the patient that helps the body fight infections and other diseases. The new immune system also has the potential to recognize and attack any remaining cancer cells in the body. The transplanted immune cells (called the "graft") identify the leukemia cells as foreign and destroy them. This is called the "graft-versus-leukemia (GVL) effect."

Allogeneic stem cell transplantation is associated with a higher rate of side effects and mortality than other treatment approaches. However, it may be considered a treatment option for patients with higher-risk ALL, based on cytogenetic and molecular test results. The decision to perform an allogeneic transplant also depends on the age of the patient and the patient's understanding of the potential benefits and risks.

Studies show that allogeneic stem cell transplantation may benefit adult ALL patients in the high-risk and intermediate-risk categories who are younger than 60 years and have an HLA-matched sibling donor. The timing of the allogeneic stem cell transplantation is one of the most important factors influencing transplant outcomes, so it is very important to start a donor search as soon as possible after diagnosis, in order to identify a suitably matched related or unrelated donor.

One possible serious side effect of allogeneic transplantation is graft-versus-host disease (GVHD). This occurs when the transplanted donor immune cells (the graft) identify the cells in the recipient's body (the host) as foreign and attack them. The parts of the body most frequently damaged by GVHD include the skin, liver, stomach, intestines and eyes. GVHD can develop within weeks after transplantation or much later. A doctor can prescribe medications that can help prevent or minimize GVHD.

Reduced-Intensity Allogeneic Stem Cell Transplantation. This type of transplantation may be a treatment option for older patients who cannot tolerate the high doses of chemotherapy and/or radiation used in preparation for a standard allogeneic stem cell transplant. This therapy reduces the number of cancer cells, but it does not completely destroy the patient's bone marrow. As in standard allogeneic transplantation, the white blood cells from the donor may recognize any remaining leukemia cells as foreign and destroy them. Also like standard allogeneic stem cell transplantation, the risk of GVHD is an important consideration and a potentially disabling side effect.

Autologous Stem Cell Transplantation. This is a procedure in which stem cells are removed from the patient before the patient undergoes intensive chemotherapy, either with or without radiation therapy. The patient's removed stem cells are stored and then returned to the patient after the treatment.

Autologous transplantation is not commonly used to treat patients who have ALL, but it may be a treatment option for ALL patients participating in a clinical trial.

Talk to your doctor about:

- Stem cell transplantation and ask whether it is a treatment option for you

For further information about stem cell transplantation, see the free LLS booklets, *Blood and Marrow Stem Cell Transplantation, Cord Blood Stem Cell Transplantation Facts* and *Graft-Versus-Host Disease.* Visit www.LLS.org/TreatmentVideos for videos about stem cell transplantation.

Treatment

Treatment Overview. Treatment for ALL typically consists of long-term multidrug chemotherapy given in three phases: induction, consolidation and maintenance. See **Figure 6** on page 36. The specific drugs, the dosages used, and timing of administration depend on several factors, including the patient's age, the specific features of the leukemia and the overall health of the patient.

Age or comorbidities (other serious health issues) may affect treatment. Doctors often give the most intensive chemotherapy regimens to patients younger than 65. However, this age limit is just a guideline. Overall health and fitness play a role. Some older patients in good health may benefit from intensive regimens or slightly less-intensive treatments. Adults who are age 65 years and older, or who have serious health conditions, may receive modified treatment regimens. There are treatments for patients of all ages.

Induction. The first phase of treatment is called "induction." The goal of induction is to destroy as many cancer cells as possible to induce (achieve) a remission. This means that leukemia cells are no longer found in bone marrow samples, and blood counts become normal. Induction therapy often lasts about 4 weeks.

Chemotherapy induction regimens for ALL generally use a combination of drugs that include **vincristine**; an anthracycline (**daunorubicin** or **doxorubicin**); and a corticosteroid (**prednisone** or **dexamethasone**), administered either with or without **pegaspargase** and/or **cyclophosphamide**. For more information on chemotherapy, see page 25.

For patients with Philadelphia chromosome-positive (Ph+ ALL), a tyrosine kinase inhibitor (TKI) such as **imatinib** or **dasatinib** is often also included. For more information on TKIs, see page 27.

Typically, the severity of the disease and the side effects of this initial therapy result in a hospital stay of 4 to 6 weeks. Some patients who live with a caregiver and near the medical facility may be safely discharged sooner. This depends on the policies of the treatment center and the status of the patient.

Central Nervous System (CNS) Prophylaxis and Treatment. ALL can spread to the central nervous system (the brain and spinal cord). At the time of diagnosis, it is uncommon for leukemia cells to be found in the central nervous system, occurring in only 3 to 7 percent of cases. However, without the routine treatment targeting the central nervous system (referred to as "CNS prophylaxis"), leukemia cells will eventually spread to the central nervous system in a large percentage of patients (50 percent or more).

CNS prophylaxis can be given to all patients throughout the entire course of ALL therapy, from induction to consolidation to the maintenance phase.

Central nervous system-directed therapy may include:

- Intrathecal chemotherapy, in which anticancer drugs are injected into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord. These drugs may include **methotrexate**, **cytarabine**, and corticosteroids (**prednisone**, **dexamethasone**).
- Systemic chemotherapy, in which anticancer drugs are given through a vein to reach any leukemia cells in the central nervous system. These drugs may include **high-dose methotrexate**, **intermediate-** or **high-dose cytarabine**, and **pegaspargase**.
- Cranial irradiation, in which radiation therapy to the brain is used to kill cancer cells.

Assessing Treatment Response. At the end of induction therapy, blood and bone marrow tests will be done to see how well your treatment is working. The doctor will check to see whether you have achieved a complete remission. A complete remission is achieved when:

- No more than 5 percent of cells in the bone marrow are blast (immature) cells
- No blasts are found in the blood
- Blood cell counts are back to normal
- All signs and symptoms of ALL are gone

If you do not achieve remission after the first course of induction chemotherapy, that may indicate the first treatment approach is unlikely to work. In this situation, a "second-line" course of treatment is given, usually using different drugs.

Minimal/Measurable Disease (MRD). Even when a complete remission is achieved, many leukemia cells that cannot be seen with a microscope may remain in the bone marrow. The presence of these cells is referred to as minimal/measurable residual disease (MRD). Patients who have achieved remission after initial treatment, but who still have MRD, are at increased risk of disease relapse. Testing for MRD can help doctors identify patients who may benefit from further treatment with intensified therapies such as allogeneic stem cell transplantation.

It is important to get tested for MRD after achieving remission. The tests used most often to detect MRD are flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing. These three tests typically use samples of bone marrow cells, but in some cases blood samples can be used. The tests are much more sensitive than standard tests that examine cell samples with a microscope.

It is often recommended that MRD testing be done after the completion of induction therapy. Recommendations for additional MRD testing depend on the treatment regimen used.

If you are in remission but test positive for MRD, your doctor may prescribe **blinatumomab (Blincyto®)**.

See *Some Drugs Used in the Treatment of ALL* starting on page 50.

See the free LLS fact sheet *Minimal/Measurable Residual Disease (MRD)* for more information.

Postremission Therapy (Consolidation and Maintenance Therapy). Postremission therapy refers to ALL treatments given to patients after their disease is in complete remission. Even when patients test negative for MRD, some residual leukemia cells that cannot be detected even with very sensitive tests are believed to remain in the body after remission. The optimal treatment for ALL patients requires additional intensive therapy after remission is achieved. As in the induction phase, individual factors such as the age of the patient, the ability to tolerate intensive treatment, cytogenetic test results, the availability of a matched stem cell donor, and other considerations may influence the decision about the best treatment approach.

Consolidation Therapy. The second phase of treatment is called consolidation therapy. This phase can also include phases known as "intensification" therapy. Consolidation therapy begins once ALL is in remission. The goal of consolidation therapy is to kill any remaining leukemia cells that could cause a relapse.

Consolidation therapy typically consists of multi-agent intensive chemotherapy. For patients with Ph+ ALL, a TKI is usually continued. In addition, most treatment plans call for the continuation of CNS prophylaxis or treatment.

The specific combination of drugs and the duration of therapy for consolidation vary. Depending on the treatment regimen used, consolidation therapy may consist of drugs that are entirely different from those used during induction, or some of the same drugs that were successful in the induction phase, either at the same or higher doses. Consolidation therapy is usually given in cycles over 4 to 6 months.

Consolidation therapy may include one or two intensified treatments like the ones used during the induction phase. These are also known as "delayed intensification" treatments.

For consolidation, several chemotherapy drugs are often combined to help prevent the leukemia cells from developing drug resistance. Some of the drugs used in the consolidation phase may include:

- High-dose **methotrexate**
- **Cytarabine**
- **Vincristine**
- **6-mercaptopurine (6-MP)**

- **Cyclophosphamide**
- **Pegaspargase**
- Corticosteroids **(prednisone, dexamethasone)**

As part of consolidation therapy, some patients in remission may receive a stem cell transplant. Doctors usually recommend stem cell transplantation for patients whose ALL has high-risk genetic features, or for patients who have high rates of MRD after initial therapy (called "persistent MRD").

Not everyone can have a stem cell transplant. It is an intense and complex treatment that can cause life-threatening side effects in some patients. Being able to have a transplant also depends on having a sufficiently matched donor and an adult caregiver. See page 29 for more information on stem cell transplantation.

Maintenance Therapy. The third phase of treatment is called maintenance therapy. The goal of maintenance therapy is to prevent disease relapse after induction therapy and consolidation therapy.

Some drugs used in the maintenance phase are given orally and patients are usually treated in an outpatient setting. Patients receive lower doses of chemotherapy drugs and, as a result, tend to have less-severe side effects. Maintenance therapy usually lasts for about 2 years.

Most maintenance therapy regimens include:

- **6-mercaptopurine** (taken once a day at home)
- **Methotrexate** (taken once a week at home)
- Periodic doses of **vincristine** (given as an IV injection in a healthcare setting) and **corticosteroids** (taken at home)

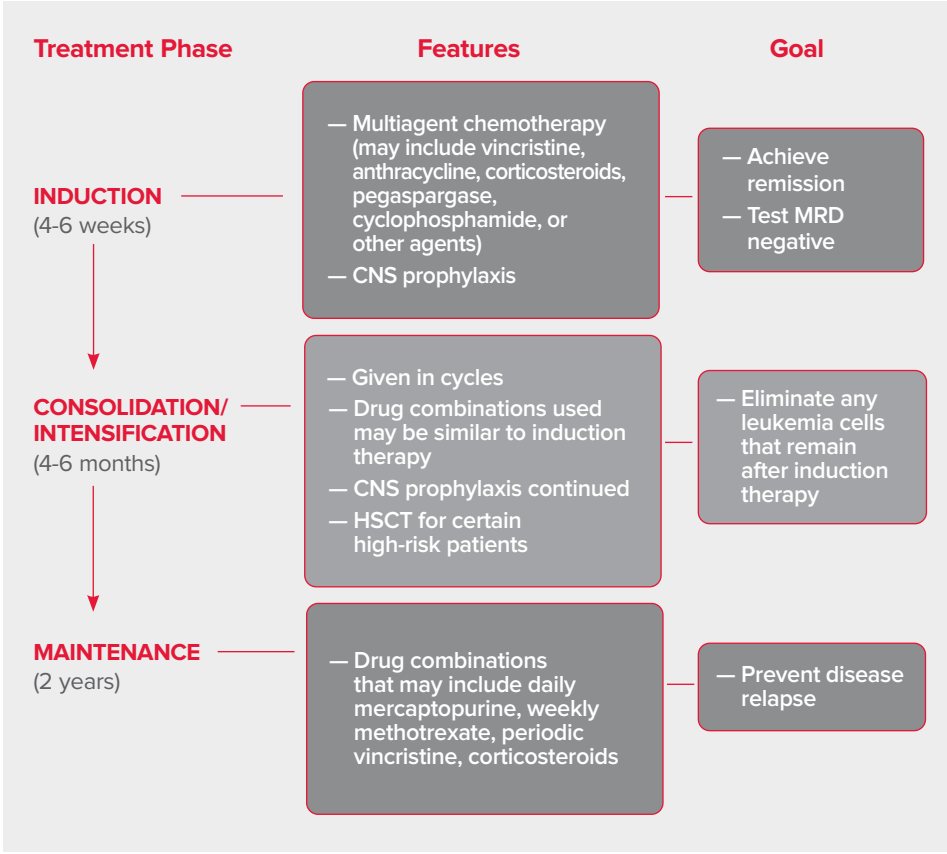
For patients with Ph+ ALL, a tyrosine kinase inhibitor (TKI) is often included during the maintenance phase as well.

If you are taking an oral medication at home, it is important for you to take the medication as prescribed by the doctor. Not taking your mediation as prescribed can increase the chance that the cancer will relapse (return).

For more information about oral drug adherence (taking medicine as prescribed), please visit www.LLS.org/booklets to see the free LLS booklet *Oral Treatment Adherence Facts.*

See *Some Drugs Used in the Treatment of ALL* starting on page 50.

Figure 6. Acute Lymphoblastic Leukemia (ALL) Treatment Overview



Abbreviations: CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease.

For a comprehensive list of ALL treatments, please see *Some Drugs Used in the Treatment of ALL* starting on page 50.

Special Treatment Considerations

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL). About 25 percent of adults with ALL have a subtype called "Ph-positive ALL" (also known as "Ph+ ALL" or "Philadelphia chromosome-positive ALL"). The leukemia cells of these patients have the Philadelphia chromosome, which is formed by a translocation between parts of chromosomes 9 and 22. A piece of chromosome 9 breaks off and attaches to chromosome 22, and a piece of chromosome 22 similarly breaks off and attaches to chromosome 9. The abnormal chromosome 22 is known as the Philadelphia chromosome. This chromosomal alteration creates

a fusion gene called *BCR-ABL1*. This gene produces a protein called a tyrosine kinase that causes the leukemia cells to grow and divide out of control.

Patients who have Ph+ ALL are typically treated with tyrosine kinase inhibitors (TKIs), combined with other medication. These combinations have become the standard of care for Ph+ ALL patients. Newer combinations of drugs for the treatment of Ph+ ALL are also being studied in clinical trials. See *Tyrosine Kinase Inhibitors* on page 27 for more information on TKIs.

Philadelphia Chromosome-like (Ph-like) ALL. About 10 percent to 30 percent of adults have a subtype of B-cell ALL with genetic features like Ph+ ALL, but without the *BCR-ABL1* fusion gene that defines Ph+ ALL. Instead, patients have a highly diverse range of genetic mutations that activate tyrosine kinase signaling. Tyrosine kinases are enzymes that play a part in many cell functions, including cell signaling, growth and division. These enzymes may become too active in leukemia cells. Tyrosine kinase inhibitors (TKIs) are drugs that work by blocking enzyme activity in a way that may prevent cancer cells from growing. Findings from recent studies that analyzed the genetic profile of patients with Ph-like ALL have suggested that using TKIs and other targeted therapies may help treat these types of leukemia.

Older Adolescents and Young Adults (AYA). The term "AYA population" generally refers to older adolescents and young adults aged 15 to 39 years. Historically, the AYA population has been treated with either a pediatric ALL regimen or an adult ALL regimen, depending on the treatment center's protocol for this age group. Adult treatment regimens and pediatric treatment regimens differ in the following ways:

- Pediatric regimens are more intense and complex than those given to older adults.
- Pediatric regimens tend to use more **pegaspargase**, **vincristine**, and corticosteroids. By contrast, adult regimens tend to use more **cyclophosphamide** and anthracyclines, such as **doxorubicin** and **daunorubicin**.
- Pediatric treatments are given for longer periods of time. Central nervous system treatment (CNS prophylaxis) is started earlier and given longer. Some children receive longer maintenance therapy than adults.

Researchers have found that AYA patients treated with pediatric protocols have improved rates of survival compared with patients of the same age who are treated with adult ALL protocols. Therefore, clinical trials are looking into the use of a variety of pediatric protocol options for AYA patients.

For more information on pediatric treatments, see the free LLS booklet *Acute Lymphoblastic Leukemia in Children and Teens.*

Treatments for Relapsed and Refractory ALL

Some patients have ALL that returns after remission. This is referred to as a "relapse" of the disease (or "relapsed ALL"). Some patients are unable to achieve a remission because their cancer does not respond to treatment. In these cases, the disease is referred to as "refractory" (or "refractory ALL").

Relapsed/refractory disease is generally more difficult to treat. But there are treatment options available. Treatment for relapsed/refractory ALL is usually more intensive or complex than the treatment used following initial diagnosis. For these reasons, it is particularly important to consider getting opinions on treatment options from someone with expertise in managing relapsed/refractory ALL.

At the time of relapse, genetic testing of the leukemia cells may be performed. The mutational pattern at the time of relapse may be different from when the disease was first diagnosed, and this can affect treatment decisions.

For patients with Ph+ ALL who did not have an adequate initial response to a TKI or who initially responded but later relapsed, the cause may be the development of a new mutation in the *BCR-ABL1* gene. A new mutation may cause the disease to become resistant to treatment and stop working. Each TKI works in a slightly different way. Certain TKIs may be able to counteract a mutation that other TKIs cannot. Testing for additional mutations in the *BCR-ABL1* gene should be done for patients who may need a different TKI.

Relapsed ALL. The goal of treatment for relapsed ALL is to achieve a complete remission again and keep the leukemia from returning. The treatment may depend on a number of factors including:

- The type of ALL (B-cell or T-cell)
- The location in the body the relapse has occurred. When the cancer returns in the bone marrow, it is called "medullary relapse." When the cancer occurs outside the bone marrow (for example, in the central nervous system or testicles), it is called "isolated extramedullary relapse"
- The amount of time that has passed between the initial diagnosis and detection of relapse. Recurrences that occur 3 years or more after diagnosis have a better prognosis and may be treated with the same induction regimen.
- The results of genetic testing of the leukemia cells
- The prior treatments the patient has received for ALL

Refractory ALL. The goal of treatment for refractory ALL is to try to attack the disease in a different way. Your doctor will use different drugs or different combinations to attain a remission and then use other therapies to increase the chances of a cure. The type of treatment will depend on:

- The type of ALL (B-cell or T-cell)
- The location in the body where the disease is persistent
- The results of genetic testing of the leukemia cells
- The prior treatments the patient has received for ALL

Treatments for Relapsed/Refractory ALL. Treatments for relapsed/refractory ALL may include:

- A clinical trial, see page 40 for more information on clinical trials
- Chemotherapy
- For patients with Ph+ ALL, a TKI given alone or as part of a chemotherapy regimen. In some cases, the TKI may be combined with a corticosteroid. If the TKI is part of a chemotherapy regimen, this regimen will usually be different from the one used during initial therapy. For some older patients who cannot tolerate chemotherapy, using a TKI along with a corticosteroid may be an option.
- **Nelarabine** for patients with T-cell ALL
- **Blinatumomab (Blincyto®)**
- **Inotuzumab ozogamicin (Besponsa®)**
- Allogeneic stem cell transplantation for physically fit patients with an available donor. Some older patients, as well as patients in poor health, may not be able to tolerate such an intense treatment.
- CAR T-cell therapy, including:
  - **Tisagenlecleucel (Kymriah®)**
  - **Brexucabtagene autoleucel (Tecartus®)**

See *Some Drugs Used in the Treatment of ALL* starting on page 50.

Talk to your doctor about:

- Therapies under study in clinical trials for refractory or relasped ALL

Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (U.S. Food and Drug Administration) requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug
  - An approved drug to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug—by mouth (pill), intravenously (IV)
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes.

Clinical trials can be difficult to navigate and figure out, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome barriers to enrollment and provide support throughout the entire clinical trial process. Our Clinical Trial Nurse Navigators are registered nurses who

are experts in blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (like past treatments, treatment responses, and your cancer genetic profile), your current health, and your medical history—because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide you and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical trial process

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers.*

Related Disease

Mixed Phenotype Acute Leukemia. Mixed phenotype acute leukemia (MPAL) is a subtype of acute leukemia, which is also known as "biphenotypic leukemia" or "mixed lineage leukemia," and has an ambiguous lineage. It is a combination of two forms of leukemia: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). It accounts for 2 to 5 percent of all acute leukemia cases, affecting patients of all ages, and there are several different subtypes. Since MPAL is rare, patients with this subtype of leukemia should seek treatment at a cancer center that has experience in treating patients with this disease. The best treatment approach for MPAL has not yet been determined. There is no standard therapy for the disease and, in general, it is associated with a poor prognosis. This is due to the difficulty in correctly identifying this type of leukemia, its low incidence, the lack of experience in treating it, and its tendency to be resistant to both ALL and AML therapies. The reasons for this resistance are not yet clear, but it may be related to the high percentage of high-risk chromosomal abnormalities found in patients with MPAL.

A variety of factors are involved in determining the best treatment for patients with MPAL. These include the patient's age, medical history (and other relevant

medical conditions), and the characteristics of the leukemia cells as determined by immunophenotyping and genetic tests. It is also important to determine whether the patient has the Philadelphia chromosome-positive (Ph+) subtype, which accounts for about 25 percent of all cases of MPAL. Treatment for Ph+ MPAL usually consists of a chemotherapy regimen for ALL based on the patient's age and in combination with a tyrosine kinase inhibitor (TKI). This may be followed by allogeneic stem cell transplantation, if needed.

For patients with a non-Ph+ subtype of MPAL, the treatment typically consists of either an ALL treatment regimen, or a combination of ALL and AML therapies. Ideally this is followed by consolidation therapy with an allogeneic stem cell transplant when a donor is available.

Side Effects and Complications of ALL Treatment

Side Effects of Chemotherapy. Most ALL treatment side effects are temporary and subside once the body adjusts to the therapy or after the therapy is completed. If side effects become severe, patients may need to be hospitalized.

Low Blood Cell Counts. Cancer and cancer treatments often cause drops in blood cell counts. This can result in a severe deficiency in the patient's number of red blood cells, white blood cells and platelets.

Transfusions of red blood cells and platelets are almost always needed for several weeks during treatment. After that, a patient's blood cell counts usually return to normal levels.

Many side effects of chemotherapy are caused by low white blood cell counts. Drugs known as "growth factors" may be given to stimulate the bone marrow to make new white blood cells, to reduce the chance for serious infections. The growth factors used most frequently are the granulocyte-colony stimulating factors such as **filgrastim (Neupogen®)** and **pegfilgrastim (Neulasta®)**.

During ALL treatment, low white blood cell counts can lead to infections from bacteria, viruses, and fungi that are normally present in the environment, on the skin, in the nose and mouth, on the gums or in the intestines. The risk of infection in patients may be increased because chemotherapy damages the cells lining the mouth and the intestines, making it easier for bacteria to enter the bloodstream. After a patient starts a course of chemotherapy, antibiotics are commonly given to prevent bacterial infection, and other drugs are given to prevent fungal and viral infections.

Because of the increased risk for infection, the medical staff, family, and friends of the patient need to practice frequent and vigorous handwashing and take other

precautions to avoid exposing patients to bacteria, viruses and other infection-causing agents. Caregivers of patients who have central lines or ports need to be meticulous when cleaning insertion sites and catheters, as instructed by their medical team.

Patients at home should seek medical attention immediately if any signs of infection develop. A temperature of 100.4°F or higher or the onset of chills may be the only sign of infection in a patient who has a very low white blood cell count. Other signs of infection may include persistent cough, sore throat, diarrhea or pain during urination.

ALL patients are advised to get certain vaccinations once they have finished their treatment, including vaccinations for pneumococcal pneumonia and influenza. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations using live organisms or with high viral loads, such as the herpes zoster or shingles vaccine, should not be administered. Patients who have ALL can receive the shingles vaccine **Shingrix®** because it is an "inactivated" rather than a "live" vaccine. COVID-19 vaccines are also recommended. Speak to your doctor for more information.

Tumor Lysis Syndrome. Patients with ALL may be at high risk for developing a condition called "tumor lysis syndrome" (TLS). This condition occurs when many cancer cells die within a short time, releasing their contents into the blood. TLS can be severe during the early phases of treatment, especially for those patients who have very high white blood cell counts before induction therapy.

TLS can occur after treatment of a fast-growing cancer like leukemia. As the leukemia cells die, they break apart and release their contents into the bloodstream, which changes the normal balance of chemicals in the blood. This can overwhelm the kidneys because they cannot get rid of the substances all at once.

Uric acid is one of the chemicals released by the dying cancer cells. Very high levels of uric acid and other chemicals can cause severe damage to the kidneys and heart. If untreated, TLS can lead to heart arrhythmias, seizures, loss of muscle control, acute kidney failure and even death. Patients with ALL are constantly monitored for the development of TLS and are given drugs such as **allopurinol (Zyloprim®)** or **rasburicase (Elitek®)** to prevent or lessen the effects of this condition.

Pain. Bone pain may occur in patients with ALL due to the infiltration of leukemia cells in the bone marrow. Some chemotherapy medicines such as **vincristine** can cause peripheral neuropathy, a nerve problem that can cause pain, numbness and tingling, usually in the hands or feet. Use of pain medications and physical therapy are very effective for patients who have pain caused by leukemia or leukemia treatment.

Other Side Effects. Chemotherapy drugs affect cells that divide quickly, which is why they work against cancer cells. They also affect healthy cells in the body that divide quickly, such as hair follicles, the lining of the intestines, and the skin. Common side effects of chemotherapy may include:

- Hair loss
- Diarrhea
- Nausea and vomiting
- Mouth sores
- Rashes
- Headaches
- Loss of appetite
- Fatigue

These short-term side effects usually go away once a patient has completed treatment. Fortunately, drugs that counteract nausea and vomiting can be given during treatment to prevent or relieve this distressing side effect.

The use of corticosteroids, such as **prednisone** and **dexamethasone,** is a main component of virtually every ALL-induction regimen. Corticosteroids are also frequently incorporated into consolidation and maintenance regimens. Side effects of corticosteroids may include hyperglycemia (high blood sugar) and corticosteroid-induced diabetes. Patients should be monitored to ensure that their glucose (blood sugar) levels are under control. The development of stomach ulcers can be another side effect of corticosteroid therapy. Medicines that reduce stomach acid, such as H2 blockers or proton-pump inhibitor drugs, may be recommended during corticosteroid therapy to decrease the risk of gastric ulceration.

There are drugs and other supportive therapies to prevent or manage side effects. **For more information, visit www.LLS.org/booklets and filter by Side Effect Management to view, print or order the free LLS series *Side Effects Management.***

Sometimes drugs or drug combinations cause side effects that continue after treatment ends. Some effects may be long-lasting (see *Long-Term and Late Effects of Treatment* below).

Long-Term and Late Effects of Treatment. While treatments for ALL have led to increased survival rates, some may cause significant long-term or late effects. Long-term effects of cancer treatment are medical problems that last for months or years after treatment ends. Late effects are medical conditions that do not appear until years, or even possibly decades, after treatment ends.

People who have been treated for ALL may be at increased risk for heart damage, other cancers, and neurologic or cognitive problems. It is important to know about the potential for long-term effects of treatment so that any problems can be identified early and managed. Various factors can influence the risk of developing long-term or late effects, including:

- Type and duration of treatment
- Age at the time of treatment
- Gender and overall health

Most ALL patients are treated with an anthracycline, such as **daunorubicin** or **doxorubicin.** Anthracyclines have been associated with increased risk for heart muscle injury or chronic heart failure. Heart disease may not become apparent until many years after treatment ends.

Osteonecrosis, also called "avascular necrosis," which is reduced blood flow to the bones, and bone pain are potential long-term side effects associated with corticosteroid therapy. Osteonecrosis often affects weight-bearing joints, such as the hip bones and/or knees. It seems to have a higher incidence among adolescents than younger children or adults and is most likely due to skeletal growth. To monitor patients who are at risk of developing osteonecrosis, routine tests to measure calcium and vitamin D levels should be done. Evaluation with imaging tests should be considered in patients who develop symptoms like joint pain.

Sometimes, cranial radiation to the brain is used for patients with obvious central nervous system (CNS) disease involvement, or those who experience CNS relapse. To avoid the risk of long-term or late effects such as neurocognitive impairment or the development of a second cancer, doctors are limiting the use of this treatment, opting for drug-therapy alternatives as much as possible.

These and other possible long-term and late effects can be managed. For more information, see the free LLS book *Navigating Life During and After a Blood Cancer Diagnosis: Adults.*

Talk to your doctor about:

- Possible long-term and late effects and follow-up care

Follow-Up Care

After you complete treatment for ALL—including maintenance therapy—and you are in remission, you will need to receive follow-up care. Patients should see a primary care doctor for a general health examination at least once a year, and should also be examined regularly by an oncologist.

Follow-up care involves regular medical check-ups. These check-ups may include blood work as well as other tests to look for signs of a relapse. The tests also check how well the patient's organs are working. This is important because ALL and its treatment can damage organs.

During the first year, a patient will undergo frequent testing, but follow-up tests are given less often during the second and third years. As time goes on, a patient may have less frequent testing and check-ups, but scheduled follow-up visits should continue indefinitely.

Each patient has a different follow-up care schedule. How often you have follow-up visits is based on your ALL subtype, your overall health, and the treatments you have received. The National Comprehensive Cancer Network (NCCN) recommends the following tests during the first 3 years after treatment ends, See **Table 4**, below.

Table 4. NCCN Recommendations for Follow-Up Exams and Tests

Year	Tests	Frequency of Tests
Year 1	• Physical exam, including testicular exam for males	Every 1 to 2 months
	• CBC with differential	Every 1 to 2 months
	• Liver function tests	Every 1 to 2 months until normal test results
Year 2	• Physical exam, including testicular exam for males	Every 3 to 6 months
	• CBC with differential	Every 3 to 6 months
Year 3 and on	• Physical exam, including testicular exam for males	Every 6 to 12 months
	• CBC with differential	Every 6 to 12 months

Other general procedures:

- Bone marrow aspiration can be considered as clinically indicated as often as 3 to 6 months for at least five years. If bone marrow aspiration is done, other tests may include: flow cytometry, cytogenetic testing, FISH, molecular testing, and MRD assessment.
- For patients with Ph+ ALL, periodic quantification testing to measure the *BCR-ABL1* gene is recommended.

Adapted from National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia 2022.

Those who have been treated for ALL are encouraged to:

- Maintain regular follow-up appointments with their hematologist-oncologist. The doctor will monitor them for signs of relapse and detect any side effects of treatment. A follow-up visit may also discover the onset of any other medical problems.
- Keep all records of your cancer diagnosis, treatments, and follow-up care. This is often called a "survivorship care plan." Ask your doctor for a written survivorship care plan. Share this information with any new healthcare providers you see. The plan should include the following information:
  - List of all healthcare providers
  - Diagnosis summary with specifics such as subtype and/or genetic markers
  - Treatment summary with specifics such as the names, dates, and dosages of chemotherapy or other drugs, site of radiation treatment, surgery and/or transplantation information, responses to treatment, and side effects
  - Maintenance treatment information, if applicable
  - List of possible late effects
  - Schedule for ongoing monitoring with recommended tests, frequency of office visits and tests, and coordinating provider(s)
  - Health and wellness recommendations such as nutrition and exercise
  - Other disease screenings and vaccinations
- Receive periodic screening and monitoring for skin, gastrointestinal, kidney, blood, bladder, prostate, breast, lung, head and neck, and other types of cancer, because of the increased risk of a second cancer associated with ALL.
- Seek medical and psychosocial support for fatigue, depression, and other long-term effects, if needed.
- Consider cancer risk-reduction strategies, such as smoking cessation, skin protection against prolonged sun exposure, healthy eating, and exercising.

You may experience difficulties when you return to your daily routines after a long period of treatment. Getting support throughout this time, and for as long as needed, is important.

For additional information about survivorship, see the free LLS booklet *Navigating Life During and After a Blood Cancer Diagnosis: Adults*.

Treatment Outcomes. The cure rates and survival outcomes for patients with ALL have improved over the past few decades. Today, nearly 90 percent of adults diagnosed with ALL achieve a complete remission, which means that leukemia cells can no longer be seen in the bone marrow with a microscope. Still, despite high remission rates, adults with ALL historically have long-term survival rates of less than 40 percent. However, these rates can vary significantly, depending on the patient's age, ALL subtype, and other prognostic factors.

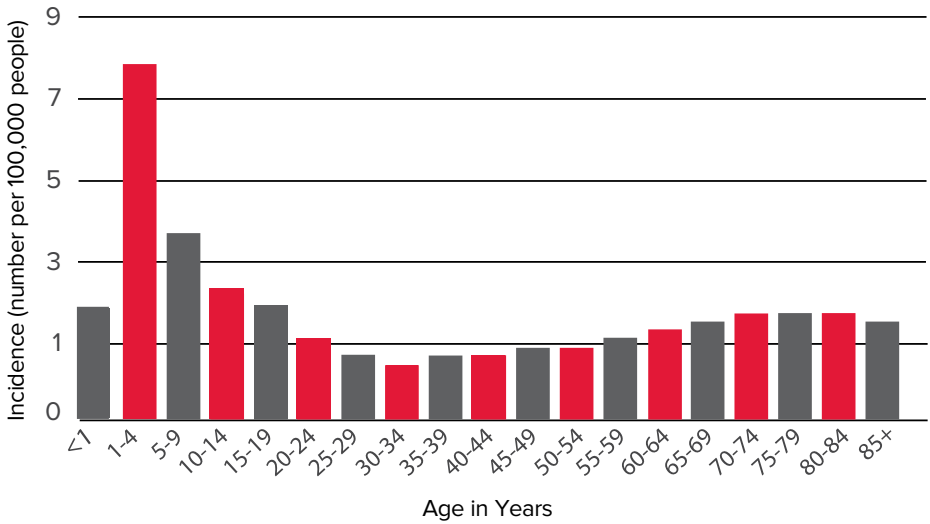
It is also important to remember that survival statistics are only estimates and are based on patients diagnosed with ALL some time ago. Since the statistics were collected, new treatments have been approved and more are being studied in clinical trials. As a result, the outlook may be better for people diagnosed with ALL today.

Incidence, Causes and Risk Factors

Incidence. Approximately 6,660 new cases of acute lymphoblastic leukemia (ALL) were expected to be diagnosed in the United States in 2022. In 2018, there were an estimated 77,711 people living with or in remission from ALL.

There is an unusual age distribution among patients with ALL. The incidence of ALL peaks between the ages of 1 and 4 years and then decreases until about age 55 years. See **Figure 7,** below.

Figure 7. Age-Specific Incidence Rates for Acute Lymphocytic Leukemia (All Races), 2014-2018



The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of ALL each year per 100,000 people, by age-group. Note that the risk of ALL is greatest in the first 5 years of life. An increase in occurrence is also seen in older individuals.
Source: SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2021 September 27]. Available from https://seer.cancer.gov/explorer/.

Causes and Risk Factors. In most cases, it is not clear what causes the genetic changes that lead to ALL. Researchers are trying to understand why these changes occur and how they cause ALL to develop. Not all patients with ALL have the same genetic mutations, and some genetic changes are more common than others. The DNA mutations associated with ALL are not usually inherited from a parent; more often they occur during a person's lifetime.

Although the cause is unknown, there are some known risk factors for ALL. A "risk factor" is anything that increases a person's chance of developing a disease. Having a risk factor, however, does not mean that a person will develop the disease. Some people with several risk factors for a disease may never develop it, while others with no known risk factors do develop it. ALL is not contagious.

Factors associated with an increased risk of developing ALL include:

- Exposure to chemotherapy and radiation therapy. People who have received certain types of chemotherapy and radiation therapy may have an increased risk of developing ALL.
- Genetic disorders. Some genetic disorders, particularly Down syndrome, are associated with an increased risk of ALL. Although rare, other genetic conditions have been categorized as risk factors for ALL. These include neurofibromatosis, Klinefelter syndrome, Fanconi anemia, Shwachman-Diamond syndrome, Bloom syndrome, Li-Fraumeni syndrome and ataxia telangiectasia. Because these are very uncommon disorders, it is highly unusual for a risk of ALL to be passed along or inherited in families.
- Age. Children and adolescents, and adults older than 70 years are at greater risk of developing ALL.
- Gender. Men are more likely than women to develop ALL.
- Race/ethnicity. In the United States, ALL is more common in Hispanics and whites.

Some Drugs Used in the Treatment of ALL

Drug Name	Administration	FDA-Approved Indications
Alkylating Agents (DNA-Damaging Drugs): These drugs work by stopping or slowing the growth of cancer cells by damaging the DNA.		
Cyclophosphamide (Cytoxan®)	Intravenous (IV) Oral	Approved for the treatment of leukemia; included in lymphodepleting regimen prior to CAR-T cell therapy
Anthracyclines: These drugs damage the DNA in cancer cells, causing them to die		
Daunorubicin (Cerubidine®)	Intravenous (IV)	Approved for treatment in combination with other anticancer drugs for remission induction of ALL in children and adults
Doxorubicin (Adriamycin®)	Intravenous (IV)	Approved for the treatment of ALL
Mitoxantrone (Novantrone®)	Intravenous (IV)	Occasionally used off-label for relapsed ALL
Antimetabolites: These drugs interfere with the normal division and functions of cancer cells		
Cytarabine (cytosine arabinoside, ARA-C; Cytosar-U®)	Intravenous (IV) Subcutaneously (under the skin) Intrathecally	Approved to be used alone or with other chemotherapy drugs to treat certain types of leukemia including ALL. Intrathecal administration of cytarabine injection (preservative free preparations only) is indicated in the prophylaxis and treatment of meningeal leukemia.
Fludarabine (Fludara®)	Intravenous (IV)	B-cell chronic lymphocytic leukemia (CLL); sometimes used prior to CAR T-cell therapy

Drug Name	Administration	FDA-Approved Indications
6-mercaptopurine (6-MP, Purinethol®, Purixan®)	Oral	Approved for the treatment of patients with ALL as part of a combination regimen
Methotrexate (Xatmep®, Abitrexate®, Trexall®)	Intravenous (IV) Intramuscular (IM) Oral	Approved for the treatment of adult and pediatric patients with ALL as part of combination chemotherapy regimen. Prophylaxis and treatment of adult and pediatric patients with meningeal leukemia
Nelarabine (Arranon®)	Intravenous (IV)	Approved for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in adult and pediatric patients age 1 year and older whose disease has not responded or has relapsed following treatment with at least two chemotherapy regimens
Enzyme Therapy: A type of treatment that uses an enzyme taken from the bacterium Escherichia coli (E. coli). It breaks down the amino acid asparagine and may block the growth of cancer cells that need asparagine to grow.		
Asparaginase Erwinia chrysanthemi (Erwinaze®)	Intramuscular (IM)	Approved as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase
Calaspargase pegol-mknl (Asparlas®)	Intravenous (IV)	Approved as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients age 1 month to 21 years

Drug Name	Administration	FDA-Approved Indications
Pegaspargase (PEG-L asparaginase, Oncaspar®)	Intramuscular (IM) Intravenous (IV)	Approved as a component of multi-agent chemotherapeutic regimen for treatment of pediatric and adult patients with: ○ First-line acute lymphoblastic leukemia ○ Acute lymphoblastic leukemia and hypersensitivity to asparaginase
Plant Alkaloids: Chemotherapy treatments made from certain types of plants. They are cell-cycle specific, meaning they attack the cancer cells during various phases of division.		
Vincristine (Oncovin®)	Intravenous (IV)	Approved for the treatment of acute leukemia
Vincristine sulfate liposome (Marqibo®)	Intravenous (IV)	Approved for treatment of relapsed/refractory ALL
Topoisomerase Inhibitor: A type of drug that blocks topoisomerases (enzymes that break and rejoin DNA strands and are needed for cells to divide and grow). Blocking these enzymes may kill cancer cells.		
Etoposide (VP-16, VePesid®, Etopophos®)	Intravenous (IV) Oral	Not approved for ALL; may be prescribed off-label as part of combination therapy
Corticosteroids: These types of drugs are made in the laboratory and is like a natural hormone that is made by the adrenal glands. Corticosteroids help destroy leukemia cells.		
Dexamethasone	Usually oral; rarely IV	Approved for the treatment of ALL
Hydrocortisone	Usually oral; rarely IV	Approved for the treatment of ALL
Prednisone	Usually oral; rarely IV	Approved for the treatment of ALL

Drug Name	Administration	FDA-Approved Indications
Tyrosine Kinase Inhibitors: These type of drugs block the enzyme tyrosine kinase, which causes stem cells to develop into more white blood cells than needed.		
Bosutinib (Bosulif®)	Oral	Approved for chronic myeloid leukemia (CML). Sometimes prescribed off-label for ALL.
Dasatinib (Sprycel®)	Oral	Approved for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) with resistance or intolerance to prior therapy.
Imatinib (Gleevec®)	Oral	Approved for the treatment of adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.
Nilotinib (Tasigna®)	Oral	Approved for CML. Sometimes prescribed off-label for ALL
Ponatinib (Iclusig®)	Oral	Approved for the treatment of Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated; or for *T315I*-positive Ph^+ ALL

Drug Name	Administration	FDA-Approved Indications
Immunotherapies: These types of drugs use substances to stimulate or suppress the immune system to help the body fight cancer.		
Blinatumomab (Blincyto®)	Intravenous (IV)	Approved for the treatment of adults and children with: ○ CD 19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% ○ Relapsed or refractory CD 19-positive B-cell precursor acute lymphoblastic leukemia (ALL)
Brexucabtagene autoleucel (Tecartus®)	Intravenous (IV)	A CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Tisagenlecleucel (Kymriah®)	Intravenous (IV)	A CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
Inotuzumab ozogamicin (Besponsa®)	ntravenous (IV)	Not currently approved to treat ALL but is being studied in clinical trials
Rituximab (Rituxan®)	Intravenous (IV)	Used off-label for treatment of ALL

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals each have a special role. They include:

- Proteins
  - Albumin. This is the most common blood protein.
  - Blood-clotting proteins (coagulation factors). They are made by the liver.
  - Erythropoietin. It is made by the kidneys and stimulates red blood cell production.
  - Immunoglobulins. These are cells that fight infection.
- Hormones, such as thyroid and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B_{12}
- Electrolytes, such as calcium, potassium and sodium

Blood Cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." See **Figure 8** on page 56. The blood cells are suspended in the plasma.

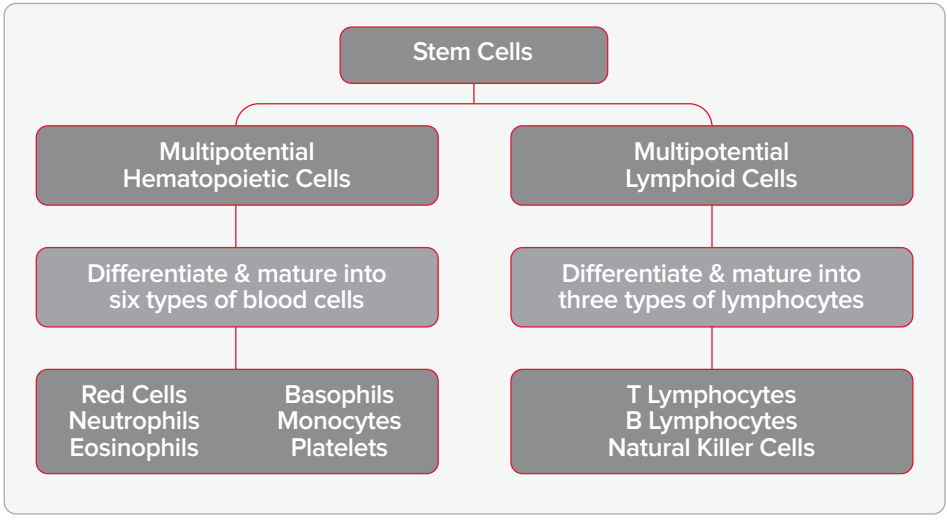
Once the blood cell is created, it will develop into one of the three types of blood cells.

These are:

1. Red blood cells are the cells that carry oxygen; they
   - Make up a little less than half of the body's total blood volume
   - Are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO_2 is removed from the lungs.
2. Platelets are cells that help blood clot; they
   - Are small cells (one-tenth the size of red blood cells)
   - Help stop bleeding from an injury or cut
   - Stick to the torn surface of the vessel, clump together, and plug up the bleeding site. They form a clot, with the help of proteins, such as fibrin, and electrolytes, such as calcium.

3. White blood cells (WBCs) are cells that fight infections. The several types of WBCs include:
    - Neutrophils and monocytes. These are “phagocytes” (eating cells) that ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
    - Eosinophils and basophils. These WBCs respond to allergens or parasites.
    - Lymphocytes. WBCs found mostly in the lymph nodes, spleen and lymphatic channels, lymphocytes are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
        - T lymphocytes (T cells)
        - B lymphocytes (B cells)
        - Natural killer (NK cells)

Figure 8. Blood Cell & Lymphocyte Development



Stem cells develop into blood cells (hematopoiesis) and lymphocytic cells.

In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the bone marrow and then circulates throughout the body.

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, bone marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the bone marrow. These stem cells are important because they can be transplanted. Some stem cells enter the bloodstream and circulate; there are not enough of them to be counted in standard blood tests. Doctors know how to stimulate the growth of these cells in the bone marrow and have them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

The Lymphatic System

The bone marrow is really two organs in one. It is:

1. The organ that forms blood cells, and it is
2. The organ that forms lymphocytes, which make up part of the immune system. Lymphocytes are found in the lymph nodes and other organs throughout the body.

The bone marrow produces three main types of lymphocytes. They are

- B lymphocytes (B cells), which make antibodies in response to foreign antigens, especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell (ingest it) along with its attached microbe. The white blood cell then kills and ingests the microbe.
- Natural killer (NK) cells, which have granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus.

The lymphocytes circulate through channels called “lymphatics,” which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system, such as the skin, spleen, tonsils and adenoids, intestinal lining, and (in young people) the thymus.

Resources and Information

LLS offers free information and services to patients, caregivers and families affected by blood cancers. This section of the book lists various resources that can be helpful to you. Use this information to learn more, to ask questions and to make the most of your healthcare team members' knowledge and skills.

For Help and Information

Consult With an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 am to 9 pm ET)
- Email or live chat: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical-trial process. Please visit www.LLS.org/CTSC for more information.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management, and survivorship nutrition. They also provide additional nutrition resources. Visit www.LLS.org/nutrition for more information and to schedule a consult.

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

Financial Assistance. LLS offers financial support including insurance premium and medication co-pay assistance as well as travel and other needs to eligible individuals with blood cancer. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Telephone/Web Education Programs. LLS offers free telephone/web and video education programs for patients, caregivers and healthcare professionals. Visit www.LLS.org/programs for more information.

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

Free Mobile Apps.

- LLS Coloring For Kids™—Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™—Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens.
Please visit www.LLS.org/SuggestedReading to view the titles.

Community Resources and Networking

LLS Community. This is the one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. Please visit www.LLS.org/chat for more information.

LLS Chapters. LLS offers support and services in the United States and Canada, including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), local support groups, local education programs and other great resources. For more information about these programs or to contact the nearest chapter, please:

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

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information:

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

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. Please visit www.LLS.org/ResourceDirectory for more information.

Additional Help for Specific Populations

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as the service of a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. Please visit www.publichealth.va.gov/exposures/agentorange or call the Department of Veterans Affairs at (877) 222-8387 for more information.

Information for Firefighters. Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit www.LLS.org/FireFighters for resources and information.

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Contact your doctor if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period.

For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter “depression” in the search box

Health Terms

Adrenal Gland. A small gland near the kidneys that makes steroid hormones. These hormones help control heart rate, blood pressure and other important body functions. They also help reduce inflammation.

Alkylating Agent. A type of chemotherapy drug used in cancer treatment. It kills cancer cells by damaging their DNA, which prevents them from dividing (reproducing).

Allogeneic Stem Cell Transplantation. A treatment that uses healthy donor stem cells to restore a patient's damaged or diseased bone marrow after receiving high doses of chemotherapy and/or radiation therapy. **See the free LLS booklet *Blood and Marrow Stem Cell Transplantation.***

Anemia. A condition in which the number of red blood cells is below normal. This results in a diminished ability of the blood to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue, and shortness of breath.

Anthracycline. A type of chemotherapy that is used to treat many types of cancer. Anthracyclines damage the DNA of cancer cells, causing them to die.

Antibody. A type of protein created by blood cells in response to an antigen (a substance that causes the body to mount a specific immune response). Antibodies help the body fight against invaders that make a person sick. Antibodies can also be made in the laboratory and are used to identify certain types of cancer and to help treat cancer.

Antigen. A substance that creates an immune response in the body, especially the production of antibodies. Examples of antigens include allergens, chemicals, bacteria, viruses, and other substances outside the body. Cells in the body, including cancer cells, also have antigens on their surfaces that can cause an immune response.

Basophil. A type of white blood cell involved in certain allergic reactions.

Biopsy. A procedure to remove a sample of cells or tissue from the body for examination by a pathologist. The pathologist may study the specimen under a microscope or perform other tests on the cells or tissue.

Blast Cell. An immature blood cell.

Blood Cell Count. A test that measures different types of cells in the blood. See Complete Blood Count.

Blood Cells. There are three types of blood cells: 1) red blood cells that carry oxygen; 2) white blood cells that fight infections; and 3) platelets that help stop bleeding.

Bone Marrow. The spongy tissue in the center of most bones, where blood cells form.

Bone Marrow Aspiration. A procedure in which a liquid sample of bone marrow is removed for examination. After the patient is given a numbing agent, a sample is taken (usually from the back of the patient's hip bone) using a special needle. Bone marrow aspiration and bone marrow biopsy are often done at the same visit, and may be done in the doctor's office or in a hospital.

Bone Marrow Biopsy. A procedure in which a sample of bone with bone marrow is removed for examination. After medication is given to numb the skin and tissue, a sample is taken (usually from back of the patient's hip bone). A special hollow biopsy needle is used to remove a core of bone containing bone marrow. Bone marrow aspiration and bone marrow biopsy are often done at the same visit, and may be done in the doctor's office or in a hospital.

CAR T-cell Therapy. See Chimeric Antigen Receptor (CAR) T-Cell Therapy.

CBC. See Complete Blood Count.

Central Line (Central Venous Catheter). A flexible tube used to deliver medications, fluids or blood products into the body or to withdraw blood samples from the body. See Port.

Central Nervous System (CNS). The brain and the spinal cord.

Central Nervous System (CNS) Prophylaxis. Treatment given to lower the risk of leukemia cells spreading to the central nervous system (brain and spinal cord). The treatment may include intrathecal chemotherapy (chemotherapy directly injected into the cerebrospinal fluid), high-dose chemotherapy injected into a vein, or radiation therapy.

Cerebrospinal fluid. Liquid that surrounds the brain and spinal cord.

Chemotherapy. Treatment that stops the growth of cancer cells by killing the cancer cells or by stopping them from dividing.

Chimeric Antigen Receptor (CAR) T-Cell Therapy. Treatment that uses a patient's own T cells (a type of white blood cell) to identify and attack cancer cells. The T cells are taken from the patient's blood and sent to a laboratory, where they are genetically modified to attack cancer cells. The engineered T cells are then multiplied and re-infused into the patient's blood stream. **See the free LLS fact sheet, *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts.***

Chromosome. Part of a cell that contains genes in a linear order. Human cells have 23 pairs of chromosomes, or a total of 46 chromosomes. **See the free LLS booklet, *Understanding Genetics.***

Clinical Trial. A carefully planned and monitored research study to evaluate how well new medical approaches work in patients. The goal of clinical trials for blood cancers is to develop new treatments, improve quality of life and increase survival.

Complete Blood Count (CBC). A laboratory test that measures the number of red blood cells, white blood cells and platelets in the blood. It also measures the amount of hemoglobin (the substance in the blood that carries oxygen) and the hematocrit (the amount of whole blood that is made up of red blood cells).

Computed Tomography (CT) Scan. A procedure in which a series of x-ray images is processed with a computer to create 3-dimensional (3-D) views of tissues and organs in the body.

Conditioning Treatment. Intensive therapy used to prepare a patient for stem cell transplantation. This treatment consists of high-dose chemotherapy with or without radiation therapy.

Conscious Sedation. A combination of medicines to help a patient relax and to block pain during a medical procedure. The patient is typically awake but will feel sleepy and likely will not remember what happened during the procedure.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes in cells. It detects chromosome alterations, and in some cases, may identify the actual genes that have been affected. These findings help doctors diagnose specific types of blood cancer, determine appropriate treatment approaches and monitor treatment response in patients.

DNA. Abbreviation for deoxyribonucleic acid, the molecules found inside cells that carry genetic information. DNA is passed to new cells during the process of cell division. A mutation (change) in the DNA can lead to cell death, changes in cell function and, in some cases, cancer.

Echocardiogram. A computer-generated picture of the heart created by bouncing sound waves (ultrasound) off internal tissues or organs of the chest. An echocardiogram shows the size, shape and position of the heart. It also shows parts inside the heart. An echocardiogram may be used to help diagnose heart problems.

Eosinophil. A type of white blood cell that is released during an infection or allergic reaction in the body.

Erythrocyte. A red blood cell. See Red Blood Cell.

Extramedullary Disease. Leukemia cells outside of the bone marrow and blood.

FDA. The abbreviation commonly used to refer to the United States Food and Drug Administration. The FDA is responsible for assuring the safety, effectiveness and security of drugs, medical devices and the nation's food supply.

FISH. See Fluorescence In Situ Hybridization (FISH).

Flow Cytometry. A test that measures certain characteristics of cells in a sample, including the size, shape and presence of tumor markers on the cell's surface. During this test, cells flow through an instrument called a "flow cytometer." When the cells pass through its laser beam, those with antibody-specific features light up and can be counted. See Immunophenotyping.

Fluorescence In Situ Hybridization (FISH). A technique for studying abnormal chromosomes in cells and tissues. Pieces of DNA that contain fluorescent molecules are added to cells or tissues on a slide. When the pieces of DNA bind to specific genes or chromosomes, they light up when viewed under a specialized microscope. This test can help diagnose some cancers, plan treatment, and monitor the effectiveness of treatment.

General Anesthesia. A combination of medication that puts a person in a sleep-like state before a surgery or other medical procedure. Under general anesthesia, a person does not feel pain because they are unconscious.

Graft-Versus-Host Disease (GVHD). A condition that occurs when cells transplanted from a donor (the graft) attack the tissues of the host (recipient). Most often, GVHD affects a patient's skin, liver and gastrointestinal tract.

Granulocyte. A type of white blood cell that has many particles (granules). Neutrophils, eosinophils and basophils are types of granulocytes.

Growth Factor. A substance made by the body that stimulates the growth of specific cells. Some growth factors are made in the laboratory and used as treatment. For example, granulocyte-colony stimulating factor (G-CSF) is a substance made in the laboratory to increase the number of neutrophils after chemotherapy.

Hematologist. A doctor who specializes in treating blood diseases.

Hematopathologist. A doctor who has special training in identifying diseases of the blood cells by examining blood, bone marrow, lymph and other tissue samples under a microscope.

Hematopoiesis. The formation of new blood cells. For more information on the blood cell development process, see *Normal Blood and Bone Marrow* on pages 55-57.

Hematopoietic Stem Cell. An immature cell that can develop into any type of blood cell including a red blood cell, a white blood cell, or a platelet.

Hemoglobin. The iron-containing substance in red blood cells that carries oxygen around the body. Hemoglobin concentration decreases when there is a reduction in the number of red blood cells. This condition is called "anemia."

Human Leukocyte Antigen (HLA). A type of protein found on cells that helps the body distinguish its own cells from foreign cells. HLA factors are inherited from a person's mother and father. HLAs make up a person's tissue type, which varies from person to person, and are a critically important factor in allogeneic (donor) stem cell transplantation. Before transplantation takes place, tissue typing is performed to determine if the donor's cells are compatible with the patient's cells.

Hyperdiploidy. In humans, cells having more than the normal 46 chromosomes.

Hypodiploidy. In humans, cells having less than the normal 46 chromosomes.

Immune System. A complex network of cells, tissues and organs that work together to defend the body against infections and diseases.

Immunophenotyping. A process that uses antibodies to identify cells based on the types of antigens (markers) on the surface of the cells. Immunophenotyping is done by a test called Flow Cytometry. See Flow Cytometry.

Immunotherapy. The term for several different treatment approaches used by doctors to use the body's immune system to treat leukemia and other diseases. These include monoclonal antibody therapy and CAR T-cell therapy.

Intrathecal Chemotherapy. Treatment in which anticancer drugs are injected into the cerebrospinal to kill any leukemia cells that may have spread to the brain and spinal cord.

Karyotype. An organized profile of a person's chromosomes. It exhibits the size, shape and number of chromosomes in a sample of cells.

Late Effect. A medical problem that either does not appear or is not noticed until years after treatment ends. Treatment-related cancer and heart disease are examples of late effects.

Leukocyte. See White Blood Cell.

Local Anesthesia. Medicine used to prevent pain to a small area of the body. The patient stays awake but has no feeling in the area of the body treated with the medicine.

Lumbar Puncture. A procedure in which a thin needle is inserted into the spinal column to collect spinal fluid or to administer anticancer drugs to the central nervous system (CNS). Another term for lumbar puncture is "spinal tap."

Lymph Node. A bean-shaped structure that is part of the body's immune system. Throughout the body, there are hundreds of lymph nodes that contain large numbers of lymphocytes, white blood cells that help fight infection and disease.

Lymphocyte. A type of white blood cell that is important to the body's immune system. There are three major types of lymphocytes: 1) B lymphocytes (B cells), which produce antibodies to help combat infections; 2) T lymphocytes (T cells), which have several functions, including assisting B lymphocytes in making antibodies; and 3) natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Lymphoid. Referring to a lymphocyte (a type of white blood cell).

Macrophage. A type of white blood cell that surrounds and kills microorganisms, eats dead cells, and helps lymphocytes with their immunity functions.

Magnetic Resonance Imaging (MRI). A test that uses magnetic fields and radio waves to create images of the body's organs and tissues.

Marrow. See Bone Marrow.

Minimal/Measurable Residual Disease (MRD). The small amount of cancer cells that may remain in the body after treatment, even when blood and bone marrow may appear to be normal. These residual cancer cells can only be identified by very sensitive tests. **See the free LLS fact sheet, *Minimal/Measurable Residual Disease*.**

Monoclonal Antibody. A type of protein that it is made in the laboratory. Monoclonal antibodies can bind to certain targets in the body, such as antigens on the surface of cancer cells. They are used in cancer treatment to target cancer cells.

Monoclonal Antibody Therapy. Targeted treatment using proteins made in the laboratory that either react with or attach to antigens on cancer cells.

Monocyte/Macrophage. A type of white blood cell that forms in the bone marrow. Some monocytes travel through the blood to tissues in the body, where they become macrophages. Macrophages can combat infection in the tissues, ingest dead cells and assist lymphocytes in immune functions.

Mutation. A change in the DNA sequence of a cell. A mutation may be caused by an error in cell division or by contact with DNA-damaging substances in the environment.

Neutropenia. A condition in which the number of neutrophils, a type of white blood cell, is below normal. People with low neutrophil counts are susceptible to infections.

Neutrophil. A type of white blood cell, and the principal type of phagocyte (microbe-eating cell), in the blood. It is the main type of cell that combats infection. People with some forms of blood cancer, or who have received treatment (such as chemotherapy) for cancer, often have low neutrophil counts.

Off-Label. The legal use of a prescription drug to treat a disease for which the drug has not been approved by the FDA.

Oncologist. A doctor who has special training in diagnosing and treating cancer.

Pathologist. A doctor who has special training in identifying diseases by studying cells and tissues under a microscope.

Petechiae. Pinhead-sized red or purple spots under the skin caused by bleeding; this may occur due to a low platelet count.

Phagocyte. A type of white blood cell that protects the body from infection by eating and killing micro-organisms, such as bacteria and fungi. Neutrophils and monocytes are the two main types of phagocytes. Once an infection occurs, phagocytes leave the bloodstream and enter the infected tissue.

Philadelphia Chromosome (Ph Chromosome). An abnormality of chromosome 22 that occurs when parts of chromosomes 9 and 22 break off and trade places. The result is a chromosome 22 that is shorter than normal. The exchange of DNA between chromosomes 9 and 22 results in the creation of a fusion gene, called *BCR-ABL1*, on chromosome 22.

Plasma. The liquid portion of the blood, in which the blood cells, platelets, proteins and various other components, are suspended. Also referred to as “blood plasma.”

Platelet. A small, colorless blood cell fragment that helps control bleeding. Platelets travel to and then collect at the site of a wound. The platelets’ sticky surfaces help them form clots at the site of the wound and stop bleeding. Also called “thrombocyte.”

Polymerase Chain Reaction (PCR). A very sensitive genetic laboratory technique that is used to detect and measure some genetic mutations and chromosomal changes that are too small to be seen with a microscope. PCR testing essentially amplifies (increases) small amounts of specific pieces of DNA so that they are easier to detect and measure. This test can find a single cancer cell among more than 100,000 healthy blood cells.

Port. A small device that enables access to a central line, which together are used to withdraw blood and administer treatments, such as intravenous fluids, drugs, and blood transfusions to patients. The port is placed under the skin, usually in the chest. It is attached to a catheter, which is a thin flexible tube that is inserted into a large vein.

Prognosis. The probable outcome or expected course of a disease; the likelihood of recovery or recurrence of disease.

Protocol. A plan for medical treatment.

Radiation Therapy. The use of x-rays and other forms of radiation to kill cancer cells.

Recurrence. The return of a disease after it has been in remission following treatment.

Red Blood Cell. A type of blood cell that contains a protein called hemoglobin. Hemoglobin carries oxygen from the lungs to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people. Also called "erythrocyte."

Reduced-Intensity Stem Cell Transplantation. A type of allogeneic stem cell transplantation in which patients receive lower doses of chemotherapy drugs and/or radiation as preparation for the transplant. This procedure may be safer than a traditional high-dose allogeneic stem cell transplant—especially for older patients. **See the free LLS booklet *Blood and Marrow Stem Cell Transplantation.***

Refractory Cancer. Cancer that does not respond to treatment.

Regimen. A treatment plan that specifies the dosage, the schedule and the duration of treatment.

Relapse. A return of disease after a period of improvement.

Remission. When signs of a disease disappear, usually following treatment.

Resistance (Resistant) to Treatment. When cancer cells continue to grow, even after administration of intensive treatments. The cancer cells may be resistant to the drug at the beginning of treatment or may become resistant after being exposed to the drug over time. Also called "drug resistance."

Risk Factor. A scientifically established factor that increases a person's chance of getting a disease. Risk factors can be classified as either genetic (inherited), lifestyle-related, or environmental.

RNA. Abbreviation for ribonucleic acid, a molecule in cells that carries out the DNA (deoxyribonucleic acid) instructions for making proteins.

Spinal Tap. See Lumbar Puncture.

Spleen. An organ in the left upper portion of the abdomen near the stomach. The spleen filters blood, stores blood cells, and destroys old blood cells. Enlargement of the spleen is called "splenomegaly."

Stem Cell. A cell from which other types of cells develop. In the bone marrow, blood-forming stem cells mature into red blood cells, white blood cells and platelets. Stem cells can be collected, preserved and used for stem cell therapy. See Hematopoiesis.

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation and Reduced-Intensity Stem Cell Transplantation.

Thrombocytopenia. A condition in which the number of platelets in the blood is below normal.

Toxin. A naturally derived substance that is poisonous to cells. A toxin can be attached to antibodies that then attach to and kill cancer cells.

Transfusion. A procedure in which whole blood or parts of blood are infused into a patient's bloodstream.

Translocation. A chromosomal abnormality in which a piece of one chromosome breaks off and attaches to another chromosome. The location at which the break occurs may affect nearby genes and lead to medical problems. See Mutation. **See the free LLS booklet *Understanding Genetics.***

Treatment cycle. A course of treatment followed by a period of rest to allow the body to recover. For example, chemotherapy given daily for 1 week followed by 3 weeks of rest might be one cycle of treatment.

Tyrosine Kinase Inhibitor (TKI). A type of drug that blocks the action of enzymes called "tyrosine kinases." Tyrosine kinases play a key role in cell function, affecting both cell growth and division. These enzymes may be too active, or found at very high levels, in some types of cancers. TKIs work to block these overactive enzymes and may stop cancer cells from growing.

White Blood Cell. A blood cell that is part of the body's immune system. The five major types of white blood cells are: neutrophils, eosinophils, basophils, monocytes and lymphocytes. Also called "leukocyte."

World Health Organization (WHO). An agency of the United Nations that deals with major health issues around the world. The WHO sets standards for healthcare and medicines and publishes scientific papers and reports.

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