

Acute Lymphoblastic Leukemia in Adults



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.



Discover what thousands already have at
www.LLS.org/Community

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

2	Introduction
3	Leukemia
4	Acute Lymphoblastic Leukemia (ALL)
6	Signs and Symptoms
7	Testing for ALL
15	Diagnosis and Cell Classification
16	Treatment Planning
22	Treatment
33	Special Treatment Considerations
36	Treatments for Relapsed and Refractory ALL
38	Clinical Trials for Blood Cancers
40	Related Disease
40	Side Effects and Complications of ALL Treatment
44	Financial Concerns
44	Follow-Up Care
47	Incidence, Causes and Risk Factors
48	Normal Blood and Bone Marrow
51	The Lymphatic System
53	Resources and Information
56	Health Terms
65	References

Acknowledgement

The Leukemia & Lymphoma Society appreciates the review of this material by:

Wendy Stock, MD

Anjali Seth Nayak Professor of Leukemia Research
Section of Hematology/Oncology
University of Chicago Medicine
Chicago, IL

Support for this publication provided by Autolus Therapeutics plc; Kite, a Gilead Company; and Takeda Oncology

This publication is designed to provide accurate and authoritative information about the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society (LLS), with the understanding that LLS is not engaged in rendering medical or other professional services. LLS carefully reviews content for accuracy and confirms that all diagnostic and therapeutic options are presented in a fair and balanced manner without particular bias to any one option.

Introduction

This booklet provides information 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 older adults, can develop ALL. This booklet discusses ALL in adults and includes information on young adults. **For information about ALL in children, see the free LLS booklet, *Acute Lymphoblastic Leukemia in Children and Teens*.**

While this booklet focuses on ALL, you may find it helpful if you have been diagnosed with a type of non-Hodgkin lymphoma called “lymphoblastic lymphoma.” This type of lymphoma starts in the same kind of cells that cause ALL. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens, rather than the kind of treatments used for other types of lymphoma.

This booklet provides information about ALL, explains tests and treatments for the disease and lists treatment options. It also provides information about clinical trials, explains normal blood and bone marrow, and defines hard-to-understand terms.

We trust that this information will provide you with a good working knowledge of ALL and that it reinforces what you already know. We hope that you will keep this booklet handy and, should you ever feel alone when confronting problems, that you will turn to it for information and guidance to find the support and resources you need.

We are here to help.

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

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

Feedback. Visit www.LLS.org/PublicationFeedback to give suggestions about this booklet.

Leukemia

Leukemia is a type of cancer. “Cancer” is a term for diseases in which abnormal cells grow uncontrollably. As cancer cells multiply, they can crowd out normal cells and make it hard for your body to work as it should. Cancer cells can also spread to other parts of the body.

Cancer can start almost anywhere in the body. Leukemia is a cancer of blood cells. It starts in cells that would normally develop into blood cells.

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.

Most blood cells are made in the bone marrow. Bone marrow is the spongy tissue in the center of most bones. Blood cells begin as hematopoietic (blood) stem cells in the bone marrow. These stem cells develop into immature cells called “blasts” that go through many stages before they eventually develop into red blood cells, white blood cells and platelets.

Leukemia is a blood cancer that begins in immature cells in the bone marrow. When one or more mutations (changes) occur in the DNA (deoxyribonucleic acid) of a blast cell, 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 copy their DNA and divide to make more and more leukemia cells. Over time, the leukemia cells crowd out and slow down the production of all the different types of normal, healthy blood cells in the bone marrow. As a result, the body does not have enough healthy red blood cells, white blood cells and/or platelets.

When this happens, the body’s organs and tissues may not receive enough oxygen to work properly due to decreased red blood cells. Also, the body may not be able to fight infections, due to decreased white blood cells, or form blood clots when they are needed, due to decreased platelets. Over time, the leukemia cells can spill out of the bone marrow into the bloodstream and spread to other parts of the body, including the brain and spinal cord, and sometimes cause enlargement of lymph nodes, the liver, the spleen and/or the testicles.

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:

- **The type of blood cell affected.** Leukemia is classified by the type of blood cell that becomes cancerous. Blood cells begin as hematopoietic (blood) stem cells in the bone marrow. A blood stem cell may become a lymphoid stem cell or a myeloid stem cell. Lymphoid stem cells develop into white blood cells called “lymphocytes.” Myeloid stem cells can develop into red blood cells, platelets or certain other types of white blood cells. Leukemia is classified as “lymphocytic” or “lymphoblastic” if it originates in a lymphoid cell. It is classified as “myeloid” or “myelogenous” if the cancerous changes start in a myeloid cell. See **Figure 6** on page 49, for an illustration of blood cell development.
- **Disease progression (how quickly or slowly the leukemia grows).** 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.

For general information about ALL, see the free LLS booklet *The ALL Guide: Information for Patients and Caregivers*.

Acute Lymphoblastic Leukemia (ALL)

Acute Lymphoblastic Leukemia (ALL). ALL is a fast-growing blood cancer in which the bone marrow makes too many immature white blood cells called “lymphoblasts.” In ALL, a mutation or a series of mutations in the DNA (genetic material) of a single lymphoid stem cell results in the formation of an abnormal lymphoblast. This abnormal lymphoblast does not develop into a healthy functioning mature lymphocyte that helps the immune system fight infections. Instead, it becomes a leukemia cell (also referred to as an “ALL cell” or a “leukemia blast”).

There are two main types of healthy lymphocytes, B cells and T cells. There are also two types of ALL, depending on the type of lymphoblast that develops into leukemia:

- B-cell ALL
- T-cell ALL

B-cell ALL is more common than T-cell ALL. In adults, B-cell ALL makes up approximately 75 percent of ALL cases; whereas T-cell ALL makes up about 25 percent of ALL cases.

Genetic errors in the leukemia cell 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 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. Once they are in the bloodstream, the leukemia cells can spread to other parts of the body such as the central nervous system (brain and spinal cord), lymph nodes, liver, spleen and testicles.

By the time ALL is diagnosed, the number of healthy red blood cells, white blood cells and platelets in the blood 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 number of red blood cells
Thrombocytopenia	Low number of platelets (“thrombocyte” is another word for platelet)
Neutropenia	Low number of neutrophils (a neutrophil is a type of white blood cell)

Lymphoblastic Lymphoma. Lymphoblastic lymphoma is a cancer of immature lymphocytes called “lymphoblasts.” It is a form of non-Hodgkin lymphoma. While most lymphomas arise from more mature lymphoid cells, in rare instances they can develop in lymphoblasts.

Lymphoblastic lymphoma can occur in either a T-cell lymphoblast, causing T-lymphoblastic lymphoma or a B-cell lymphoblast, causing B-lymphoblastic lymphoma. These are the same types of cells that cause ALL. The main difference between ALL and lymphoblastic lymphoma is the location of the cancer cells. Leukemias such as ALL affect the bone marrow and sometimes the blood. If the bone marrow has 20 percent or more lymphoblasts, the disease is considered to be leukemia. In contrast, if the lymphoblasts are restricted to a mass in a lymph node or other lymphatic tissue with less than 20 percent of lymphoblasts in the bone marrow, than it is considered to be lymphoblastic lymphoma.

T-lymphoblastic lymphoma is more common than B-lymphoblastic lymphoma. T-lymphoblastic lymphoma often starts in the thymus, located in the upper chest area called the “mediastinum.” In B-lymphoblastic lymphoma, B-cell lymphoblasts are often found in the lymph nodes.

Lymphoblastic lymphoma is very rare in older adults. It mostly affects younger people in their late teens or early twenties. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than treatments used for other forms of lymphoma and should seek treatment at a cancer center that has experience in treating lymphoblastic lymphoma and ALL.

For information about non-Hodgkin lymphoma, see the free LLS booklet *Non-Hodgkin Lymphoma*.

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. In some large medical centers, there are hematologist-oncologists who specialize in treating acute leukemias such as ALL.

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. As a result, patients with ALL may not have enough mature red blood cells, white blood cells and/or platelets, so they 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 or purple 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
- Swollen gums

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.

Testing for ALL

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

To diagnose ALL, doctors use a variety of tests to analyze blood and bone marrow cells. A pathologist—a doctor who specializes in identifying diseases by studying cells under a microscope—will examine the blood cells and the bone marrow cells. The samples should also be examined by a hematopathologist, a pathologist who specializes in diagnosing blood and bone marrow diseases.

The following are some of the tests done to diagnose ALL. Some of these tests may be repeated both during and after treatment to evaluate if treatment is working.

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. Your 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. In addition to the blood and bone marrow, leukemia cells can sometimes be found in lymph nodes and other organs in the body such as the liver, spleen

and testicles. 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, and 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 or swelling.

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, a protein inside red blood cells that carries oxygen from the lungs to tissues in the body. 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—immature lymphoblasts that do not protect against infection. Meanwhile, they may not have enough mature red blood cells, white blood cells or platelets.

If the CBC results 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 examining a sample of bone marrow cells.

Bone Marrow Aspiration and Biopsy. Leukemia starts in the bone marrow, the spongy tissue inside the center of most bones. When blood tests show cytopenias (low blood cell counts) or the presence of blast cells (immature cells) in the blood, your doctor may recommend a bone marrow aspiration and biopsy to see whether your bone marrow is healthy and making normal amounts of blood cells. Doctors use the results from these tests to diagnose and monitor blood and bone marrow diseases, including leukemia.

Bone marrow has both a liquid and a solid component.

- A bone marrow aspiration is a procedure to remove a sample of the liquid part of the bone marrow.
- A bone marrow biopsy is a procedure to remove a small sample of the solid, spongy part of the bone marrow.

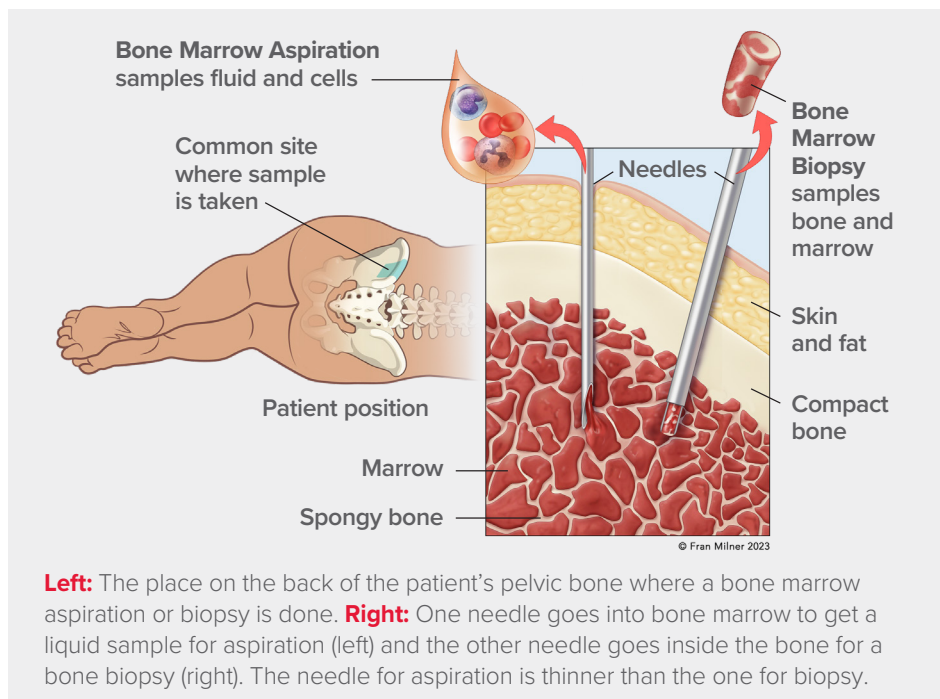
Many people will have both tests at the same time, but sometimes they just have a bone marrow aspiration. Bone marrow aspiration and biopsy are often performed at the doctor's office or the hospital. Both samples are usually taken from the large hip bone in the lower back. You will likely lie on your stomach or side.

For many patients, this is a painful procedure, so you will receive medicine to numb the skin and the surface of the bone. You may also have the option to take medicine before the procedure to help you relax. Some patients may be given a sedative so that they will feel less pain and have no memory of the procedure.

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 a solid piece of bone marrow. Both needles are inserted through the skin, generally in the same area. Both bone marrow samples are sent to the laboratory where they are examined under the microscope. See **Figure 1** below for an illustration of the bone marrow tests.

Figure 1. Bone Marrow Aspiration and Biopsy



Left: The place on the back of the patient's pelvic bone where a bone marrow aspiration or biopsy is done. **Right:** One needle goes into bone marrow to get a liquid sample for aspiration (left) and the other needle goes inside the bone for a bone biopsy (right). The needle for aspiration is thinner than the one for biopsy.

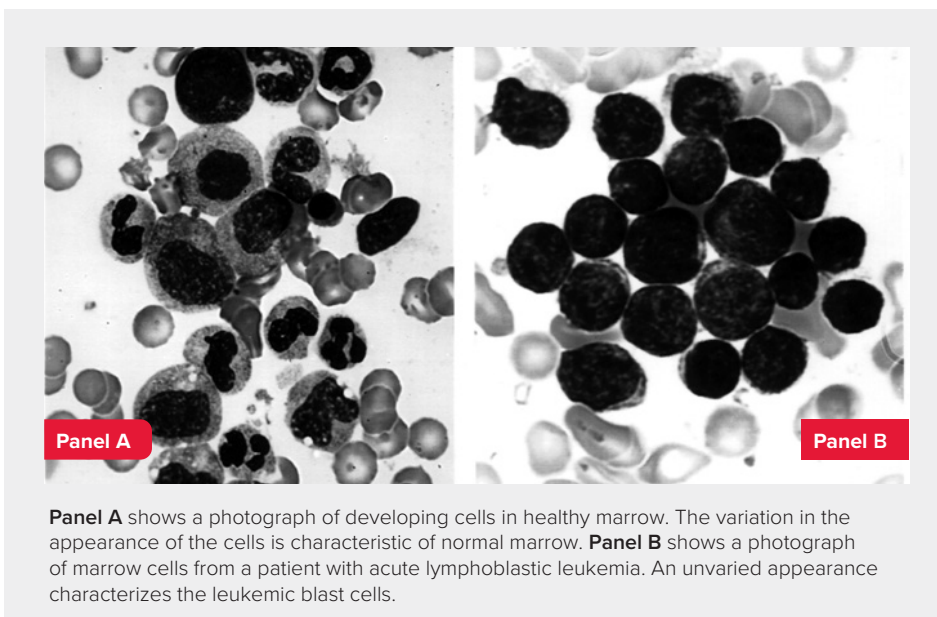
Visit www.LLS.org/3D to view an interactive 3D model that will help you visualize and better understand the bone marrow aspiration and biopsy procedures.

Both samples are sent to the laboratory where they are examined under a microscope. The various types of white blood cells, red blood cells and platelets are counted and examined to check their composition and determine whether the cells look abnormal (see **Figure 2**, on page 10).

The hematopathologist also determines the percentage of blast cells in the bone marrow. In normal healthy bone marrow, there are typically no more than 5 percent blast cells. Generally, a diagnosis of ALL in adults requires a finding of 20 percent or more lymphoblasts in the bone marrow. 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 does not necessarily indicate a poorer prognosis (the likely outcome of the disease).

If leukemia is diagnosed, additional tests are done on the blood and bone marrow samples to gather information about the subtype of ALL.

Figure 2. Normal Cells vs. Acute Lymphoblastic Leukemia (ALL) Cells



Biomarker Testing. These laboratory tests examine the cancer cells from the blood, bone marrow, lymph nodes or other tissues to check for certain genes, proteins or other molecules to provide information about a person's cancer. Each person's cancer has a unique pattern of biomarkers.

Biomarker testing may also be used to help plan treatment, find out how well treatment is working or predict whether cancer will come back or spread to other parts of the body. Biomarker tests for ALL include:

Immunophenotyping (Flow Cytometry). This lab test identifies cancer cells based on markers called "antigens." Antigens are proteins found either on the surface or within white blood cells. Finding (or not finding) certain antigens can help determine the type of leukemia. 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 on blast cells from the blood, lymph nodes and other tissues.

Immunophenotyping is done with an instrument called a "flow cytometer." A flow cytometry test can count the number of cells in a sample, as well as measure 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 antigens 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 have different antigens on their surfaces, depending on the type of leukemia. These antigens, called “cluster of differentiation (CD),” help further identify the type of leukemia cells. 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 antigens:

- B-cell ALL lymphoblasts typically express CD10, CD19, CD22 and CD79a on their surfaces. CD20 may also be expressed in approximately 30 to 40 percent of B cells in adults with ALL.
- T-cell ALL lymphoblasts typically express CD1a, CD2, CD3, CD5 and CD7.

These markers are important in distinguishing B-cell ALL from T-cell ALL. In addition, many of the most successful new treatments target a specific marker, CD19, on the cell surface of the lymphoblast.

In addition to diagnosis, flow cytometry is also used after treatment for evaluating measurable residual disease (MRD). This refers to the small number of cancer cells that may remain in the body after treatment. Flow cytometry can find one cancer cell among 10,000 to 100,000 normal bone marrow cells. Testing for MRD helps doctors plan additional treatments. It is also used to find out how well treatment is working. For more information on MRD, see page 30.

Cytogenetic Analysis (Karyotyping). 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.” In people with ALL, cytogenetic analysis is used to look for abnormal changes in the structure of the chromosomes within the 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. See **Figure 3** on page 12, for an illustration of a normal karyotype.

In many cases of ALL, the chromosomes of leukemia cells have abnormal changes that can be seen under a microscope. Cytogenetic testing can be done on leukemia cells from either a bone marrow sample or a blood sample. The leukemia cells in the sample are allowed to grow in the laboratory and then are stained. 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.

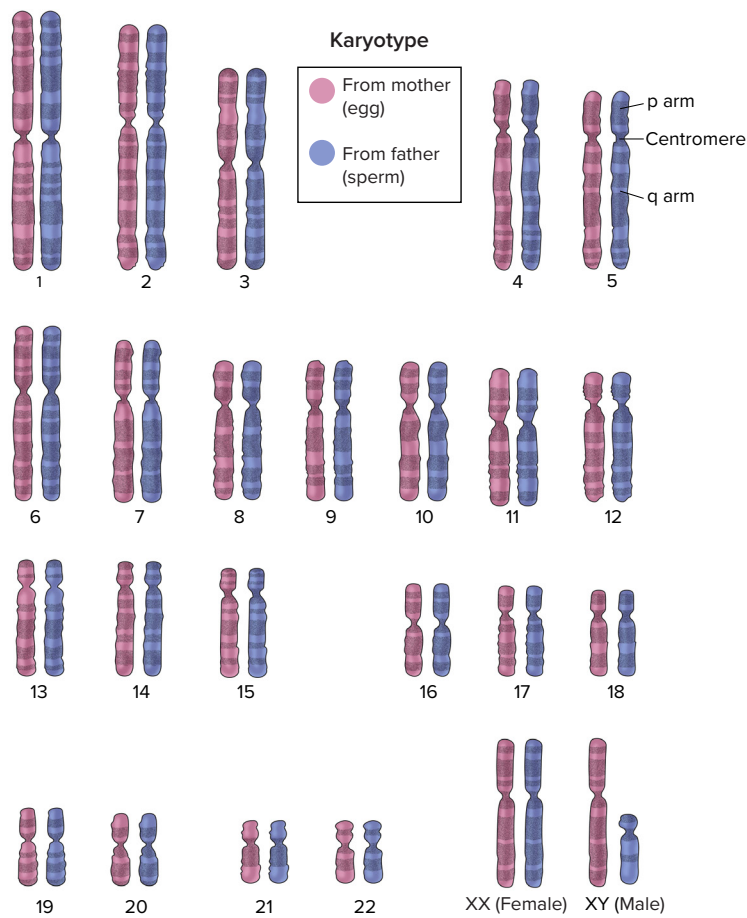
Translocations are the most common type of genetic change associated with ALL. In a translocation, the DNA from one chromosome breaks off and becomes attached to a different chromosome. Sometimes pieces from two different chromosomes trade places. A translocation may result in a “fusion gene,” an abnormal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

Another type of genetic change that occurs in ALL is a “numerical abnormality.” A numerical abnormality is either an increase or decrease 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 leukemia cells.

About 75 percent of adults with ALL 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 **Table 1** on page 14 for a list of common chromosomal abnormalities in ALL.

Cytogenetic analysis provides information for determining a patient’s prognosis 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. See page 33 for more information on Ph+ ALL.

Figure 3. Normal Karyotype



© Fran Milner 2020

Fluorescence In Situ Hybridization (FISH). Doctors use this very sensitive test 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 abnormal chromosome 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 another very sensitive lab test. Doctors use it to detect and measure certain genetic mutations and chromosomal changes within the leukemia cells 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 to 1 million healthy cells. PCR testing is another method used to determine a patient’s measurable residual disease (MRD)—the small amount of cancer cells that may remain in the body after treatment. PCR can be done with either a bone marrow sample or a blood sample.

Next-Generation Sequencing (NGS). Next-generation sequencing, also called “molecular testing” or “genomic testing,” refers to a number of different laboratory tests that examine the exact sequence (order) of DNA or RNA. This makes it possible to identify a variety of genetic changes in a patient’s cancer cells. These changes are important in guiding risk assessment and prognosis and may also inform treatment decisions for targeted therapy specific to the particular change in the genetic sequence of the leukemia cell. The information these tests provide can help doctors to determine which patients are at high risk and may need more intensive treatment or may benefit from treatment with new therapies. See **Table 1** on page 14 for a list of genetic abnormalities in ALL.

There are targeted sequencing tests (also called “multigene panels”) that look for specific mutations in the cancer cells. These tests focus on specific sets of genes or areas of DNA. There are also broad DNA sequencing tests (genomic screening tests) that analyze the sequence of large regions of DNA, rather than looking for mutations of specific genes. Doctors may also order sequencing of all the DNA in the cancer cells, and/or normal cells in the body. This test is known as “whole genome sequencing.”

The term “next-generation sequencing (NGS)” is a catch-all term that describes a number of different modern sequencing technologies. These technologies allow for sequencing of DNA and RNA much more quickly and cheaply than sequencing methods that were used previously.

Next-generation sequencing may be done when the cancer is first diagnosed and is also used after treatment for evaluating measurable residual disease (MRD). It can find one leukemia cell among one million normal bone marrow cells.

See the free LLS booklets *Understanding Genetics, Biomarker Testing for Cancer Treatment* and *Understanding Lab and Imaging Tests* for more information about these tests.

Table 1. Common Chromosomal and Gene Abnormalities in ALL

Cytogenetics	Gene	Frequency in Adults
Hyperdiploidy (>50 chromosomes)	—	7%
Hypodiploidy (<44 chromosomes)	—	2%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	<i>BCR::ABL1</i>	25%
t(12;21)(p13;q22)	<i>ETV6::RUNX1 (TEL::AML1)</i>	2%
t(v;11q23) [eg, t(4;11) and others], t(11;19)	<i>KMT2A rearranged</i>	10%
t(1;19)(q23;p13)	<i>TCF3::PBX1 (E2A::PBX1)</i>	3%
t(5;14)(q31;q32)	<i>IL3::IGH</i>	< 1%
t(8;14), t(2;8), t(8;22)	<i>c-MYC</i>	4%
t(1;14)(p32;q11)	<i>TAL-1^a</i>	12%
t(10;14)(q24;q11)	<i>HOX11 (TLX1)</i>	8%
t(5;14)(q35;q32)	<i>HOX11L2^a</i>	1%
t(11;14)(q11)[eg, (p13;q11), (p15;q11)]	<i>TCRα</i> and <i>TCRσ</i>	20%-25%
<i>BCR::ABL1</i> -like/Ph-like	various	10%-30%
B-ALL with iAMP21	<i>RUNX1</i>	—
Early T-cell precursor (ETP)	various ^a	2%
Ikaros	<i>IKZF1</i>	25%-35%

^a Abnormalities observed exclusively in T-cell ALL; all others occur exclusively or predominantly in B-cell ALL. Abbreviations: iAMP21, intrachromosomal amplification of chromosome 21; p, the short arm of a chromosome (the upper half); q, the long arm of a chromosome (the lower half); t, a translocation between chromosomes. Adapted from NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. 2024.

Diagnosis and Cell Classification

In general, for a diagnosis of ALL, there must be 20 percent or more lymphoblasts in the bone marrow. The World Health Organization (WHO) classifies ALL based on the following:

- The types of lymphocytes affected (B cell vs T cell); and
- The specific gene or chromosomal changes to the leukemia cells

See **Table 2** below for the WHO’s most recent classification of ALL.

Table 2. World Health Organization Classification of Acute Lymphoblastic Leukemia (ALL)

B-cell lymphoblastic leukemias/lymphomas
B-lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)
B-lymphoblastic leukemia/lymphoma with high hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with iAMP21
B-lymphoblastic leukemia/lymphoma with <i>BCR::ABL1</i> fusion
B-lymphoblastic leukemia/lymphoma with <i>BCR::ABL1</i> -like features
B-lymphoblastic leukemia/lymphoma with <i>KMT2A</i> rearrangement
B-lymphoblastic leukemia/lymphoma with <i>ETV6::RUNX1</i> fusion
B-lymphoblastic leukemia/lymphoma with <i>ETV6::RUNX1</i> -like features
B-lymphoblastic leukemia/lymphoma with <i>TCF3::PBX1</i> fusion
B-lymphoblastic leukemia/lymphoma with <i>IGH::IL3</i> fusion
B-cell lymphoblastic leukemia/lymphoma with <i>TCF3::HLF</i> fusion
B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities
T-lymphoblastic leukemia/lymphoma
T-lymphoblastic leukemia/lymphoma, NOS
Early T-precursor lymphoblastic leukemia/lymphoma

Source: Alaggia R, Amador C, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720-1748.

Note that before 2008, the WHO called B-cell lymphoblastic leukemia “precursor B-lymphoblastic leukemia.” This older term was 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*.**

Determination of your ALL subtype is an important factor in treatment planning. Based on your ALL subtype, you and your doctor will discuss your treatment options.

Treatment Planning

Choosing a Hospital and Doctor. When you find out that you have cancer, you want to get the best possible medical care and treatment. ALL is an aggressive blood cancer that can be difficult to treat. 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 have significant experience in the care of patients with ALL.

Typically, ALL patients need to start treatment very soon 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. A hematologist-oncologist 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 at (800) 955-4572 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. Cancer treatments, including some chemotherapy drugs, radiation and surgery, may affect fertility (the ability to have children in the future). Changes to fertility, which can happen to both males and females, may be temporary or permanent. Before you begin your ALL treatment, it is important to talk with your doctor about whether your treatment could affect your fertility.

Those who want to have children in the future 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 cancer treatment to address fertility options may not always be recommended. You may need to start treatment right away. Even if you must start treatment immediately, a fertility specialist may still be able to help preserve your fertility after you have finished induction therapy and before you continue on with additional intensive post-remission therapies.

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. A blood chemistry test indicates how well a person's kidneys, liver and other organs are working. It also provides helpful information about any potential organ damage caused by leukemia cells or cancer treatments.
- **Liver Function Tests.** Liver function tests check how well the liver is working. 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. In addition, some chemotherapy drugs can damage the liver, which can also affect liver function.
- **Coagulation Tests.** Coagulation (blood clotting) prevents excessive bleeding from a cut or injury. But if blood clots form inside of blood vessels, they can become dangerous. Coagulation tests measure the blood's ability to clot and how long it takes. 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 fibrinogen, a protein that helps blood clot.
- **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,

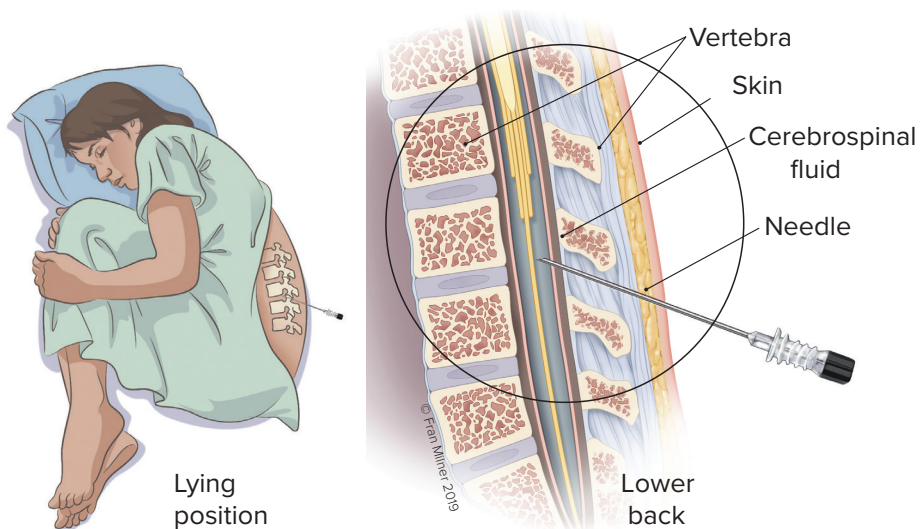
especially if white blood cell counts are very high before beginning therapy. A TLS panel can help your doctor assess if you are likely to get TLS or if you already have it.

- **HLA Typing.** This blood test identifies certain proteins, called human leukocyte antigens (HLAs), found on the surface of most cells in the body. HLAs 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 allogeneic stem cell transplantation, see page 31.

Lumbar Puncture. ALL can spread to the fluid that flows around the brain and spinal cord, called the "cerebrospinal fluid." To determine whether leukemia cells have spread to this area, a sample of the cerebrospinal fluid is collected in a procedure called a "lumbar puncture" or "spinal tap."

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** below. 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 alone. If lymphoblastic lymphoma is suspected, a “whole-body” PET/CT scan is recommended.
- **Magnetic Resonance Imaging (MRI).** 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 are leukemia cells in the testicles.

Heart Tests. Some cancer treatments can cause heart problems. Most patients with ALL are treated with chemotherapy drugs called “anthracyclines.” These drugs have been associated with increased risk for heart muscle injury or chronic heart failure. Before treatment starts, your doctor may order tests to ensure that your heart is healthy enough to proceed. They will also want to monitor your heart during and after treatment. Testing of the heart may include:

- **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.

- **MUGA (multigated acquisition) Scan.** This is a highly accurate test used to determine how well the heart is pumping blood. A small amount of radioactive tracer is injected into a vein. The tracer attaches to red blood cells and passes through the heart. A special camera that can detect the tracer creates a video of the blood pumping through the heart.

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 their cancer. These are called “prognostic factors.” Doctors use prognostic factors to help predict how a person’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, and if so, when to perform the transplant.

Prognostic factors for adults with ALL include:

- **Age.** Younger adults have a better prognosis than adults older than 35 years. The leukemia cells in older patients tend to be more resistant to treatment, and older adults also have a harder time tolerating intensive chemotherapy.
- **White blood cell count.** Patients with a lower white blood cell count (less than 30,000/microliter for B-cell ALL and less than 100,000/microliter 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 21 for genetic 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 and Molecular Prognostic Risk Groups for B-Cell ALL

Risk Groups	Genetics
Standard 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): <i>ETV6::RUNX1</i> ○ t(1;19)(q23;p13.3): <i>TCF3::PBX1</i> ○ <i>DUX4</i> rearranged ○ <i>PAX5</i> P80R ○ t(9;22)(q34;q11.2): <i>BCR::ABL1</i> without <i>IKZF1</i> plus and without antecedent chronic myeloid leukemia (CML)
Poor risk	○ Hypodiploidy (<44 chromosomes) ○ <i>TP53</i> mutation ○ <i>KMT2A</i> rearranged (t[4;11] or others) ○ <i>IgH</i> rearranged ○ <i>HLF</i> rearranged ○ <i>ZNF384</i> rearranged ○ <i>MEF2D</i> rearranged ○ <i>MYC</i> rearranged ○ t(9;22)(q34;q11.2): <i>BCR::ABL1</i> ○ <i>BCR::ABL1</i>-like (Philadelphia chromosome [Ph]-like) ALL ▶ JAK-STAT (<i>CRLF2r</i>, <i>EPORr</i>, <i>JAK1/2/3r</i>, <i>TYK2r</i>, mutations of <i>SH2B3</i>, <i>IL7R</i>, <i>JAK1/2/3</i>) ▶ ABL class (rearrangements of <i>ABL1</i>, <i>ABL2</i>, <i>PDGFRA</i>, <i>PDGFRB</i>, <i>FGFR</i>) ▶ Other (<i>NTRKr</i>, <i>FLT3r</i>, <i>LYNr</i>, <i>PTK2Br</i>) ○ <i>PAX5alt</i> ○ t(9;22)(q34;q11.2): <i>BCR::ABL1</i> with <i>IKZF1</i> plus and/or antecedent CML ○ Intrachromosomal amplification of chromosome 21 (iAMP21) ○ Alterations of <i>IKZF1</i> ○ Complex karyotype (5 or more chromosomal abnormalities)

Abbreviations: ALL, acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor; 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: Adapted from National Comprehensive Cancer Network (NCCN) Acute Lymphoblastic Leukemia Guidelines. 2024.

Treatment

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

Treatment Overview. Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. A clinical trial is a type of research study that tests how well new medical approaches work in people. 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. For more information on clinical trials, see page 38.

Talk to your doctor about:

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

The goal of treatment is not only to achieve a remission but also to prevent the disease from coming back. Not everyone with ALL receives the same treatment. Your doctor will tailor your treatment based on your ALL subtype and other factors such as your age and overall health.

Age and comorbidities (other serious health issues) may affect treatment. Doctors often give the most intensive chemotherapy regimens to patients younger than age 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.

The current standard treatment for ALL often consists of long-term multidrug chemotherapy given in three phases: induction, consolidation and maintenance. It usually takes between 2 and 3 years to complete. It is often intense, especially in the first few months of treatment. The longest phase, maintenance, lasts about 2 years, during which people are often able to return to work or school.

Treatment may also include targeted therapy, stem cell transplantation, immunotherapy, and/or a treatment called “CAR T-cell therapy.” See **Table 4, Drug Classes and Drug Mechanisms** on page 23 and **Table 5, Some Drugs Used in the Treatment of ALL** on page 24. The specific drugs, dosages and timing of administration depend on several factors, including the patient’s age, the specific genetic features of the leukemia cells and the overall health and level of fitness of the patient.

Table 4. Drug Classes and Drug Mechanisms

Alkylating Agents (DNA-Damaging Drugs)	Chemotherapy drugs that prevent cells from reproducing (dividing) by damaging the DNA in the cells.
Anthracyclines	Chemotherapy drugs that are derived from certain types of <i>Streptomyces</i> bacteria. Anthracyclines work by damaging the DNA of cancer cells, which causes them to die before they can multiply.
Antibody-Drug Conjugates	Substances made up of monoclonal antibodies chemically linked to a drug. The monoclonal antibody binds to specific proteins or receptors found on certain types of cells, including cancer cells. The linked drug enters these cells and kills them without harming other cells.
Antimetabolites	Chemotherapy drugs that interfere with the normal division and function of cancer cells. Antimetabolites mimic the building blocks of DNA or RNA that cancer cells need to survive and grow. When the cancer cell uses an antimetabolite instead of the natural substances, it cannot produce normal DNA or RNA and the cell dies.
Asparaginase-Specific Enzyme Therapies	The enzyme asparaginase interferes with natural substances necessary for cancer cell growth.
Bispecific T-Cell Engagers (BiTEs)	BiTEs are monoclonal antibody therapies that attach to two different proteins at the same time. One attaches to a protein on B cells including some leukemia and lymphoma cells. Another attaches to a protein on immune cells called T cells. By binding to both of these proteins, the drug brings the cancer cells and immune cells together, which causes the immune system to attack the cancer cells.
Chimeric-Antigen Receptor (CAR) T-Cell Therapies	A type of immunotherapy that consists of modifying a patient's own immune cells to recognize and attack cancer cells.
Corticosteroids	Corticosteroids are hormones that can kill lymphocytes. They are believed to work by blocking cell metabolism through their effect on specific genes. In high doses, these synthetic hormones—relatives of the natural hormone cortisol—can kill leukemia cells.
Monoclonal Antibodies	Monoclonal antibodies are laboratory-produced proteins that target specific antigens on the cancer cell's surface to interfere with the cell's function and destroy it. Once the antibody finds and attaches to its target, it can "recruit" (harness) other parts of the immune system to destroy cells that contain the antigen.
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.
Proteasome Inhibitors	These drugs block the actions of proteasomes (proteins) that allow the leukemia cells to survive.
Topoisomerase Inhibitors	Drugs that block topoisomerases (enzymes that break and rejoin DNA strands and are needed for cells to divide and grow). Blocking these enzymes may kill cancer cells.
Tyrosine Kinase Inhibitors (TKIs)	TKIs are substances that block the action of enzymes called tyrosine kinases. Tyrosine kinases are a part of many cell functions, including cell signaling, growth and division. These enzymes may be too active or found at high levels in some types of cancer cells, and blocking them may help keep cancer cells from growing.

Table 5. Some Drugs Used in the Treatment of ALL

For more information, see the package insert and/or the full prescribing information for each medication (available on the internet).

Drug Name Type of Drug Administration	Indications
6-mercaptopurine (6-MP, Purinethol®, Purixan®) Antimetabolite Oral	Approved for the treatment of patients with ALL as part of a combination maintenance regimen
Asparaginase Erwinia chrysanthemi (Erwinaze®) Enzyme Therapy Intramuscular (IM) Intravenous (IV)	Approved as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to <i>E. coli</i> -derived asparaginase
Blinatumomab (Blinicyto®) Bispecific T-cell Engager (BiTE) Intravenous (IV)	Approved for the treatment of adults and children with: • CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% • Relapsed or refractory CD19-positive B-cell precursor ALL
Bortezomib (Velcade®) Proteasome Inhibitor Intravenous (IV) Subcutaneous Injection	Approved for the treatment of adult patients with multiple myeloma and mantle cell lymphoma. Used as an off-label treatment for T-cell ALL.
Brexucabtagene autoleucel (Tecartus®) Chimeric Antigen Receptor (CAR) T-Cell Therapy Intravenous (IV)	Approved for the treatment of adult patients with relapsed or refractory B-cell precursor ALL
Calaspargase pegol-mknl (Asparlas®) Enzyme Therapy 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
Cyclophosphamide (Cytosan®) Alkylating Agent Intravenous (IV) Oral	Approved for the treatment of leukemia; included in lymphodepleting regimen prior to CAR-T cell therapy

Drug Name Type of Drug Administration	Indications
Cytarabine (cytosine arabinoside, ARA-C; Cytosar-U®) Antimetabolite Intravenous (IV) Subcutaneous injection	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 leukemia in the cerebrospinal fluid.
Dasatinib (Sprycel®) Tyrosine Kinase Inhibitor (TKI) Oral	Approved for the treatment of adults with Philadelphia chromosome-positive ALL (Ph+ ALL) with resistance or intolerance to prior therapy.
Daunorubicin (Cerubidine®) Anthracycline Intravenous (IV)	Approved for treatment in combination with other anticancer drugs for remission induction of ALL in children and adults
Dexamethasone Corticosteroid Usually oral Rarely Intravenous (IV)	Approved for the treatment of ALL
Doxorubicin (Adriamycin®) Anthracycline Intravenous (IV)	Approved for the treatment of ALL
Hydrocortisone Corticosteroid Oral Intravenous (IV) Intramuscular (IM) Intrathecal	Approved for the treatment of ALL
Imatinib (Gleevec®) Tyrosine Kinase Inhibitor (TKI) Oral	Approved for the treatment of adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
Inotuzumab ozogamicin (Besponsa®) Antibody-Drug Conjugate Intravenous (IV)	Approved for the treatment of relapsed or refractory CD22-positive B-cell precursor ALL in adult and pediatric patients 1 year and older

Drug Name Type of Drug Administration	Indications
Methotrexate (Abitrexate®, Trexall®) Antimetabolite Intravenous (IV) Intramuscular (IM) Oral Intrathecal	Approved for the treatment of adult and pediatric patients with ALL as part of combination chemotherapy regimen; Intrathecal administration is approved for the prophylaxis and treatment of adult and pediatric patients with meningeal leukemia.
Nelarabine (Arranon®) Antimetabolite 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
Ofatumumab (Kesimpta®) Monoclonal Antibody Injection	Used off-label for the treatment of ALL
Pegaspargase (PEG-L asparaginase, Oncaspar®) Enzyme Therapy Intramuscular (IM) Intravenous (IV)	Approved as a component of a multi-agent chemotherapeutic regimen for treatment of pediatric and adult patients with: • First-line ALL • ALL and hypersensitivity to asparaginase
Ponatinib (Iclusig®) Tyrosine Kinase Inhibitor (TKI) Oral	Approved for the treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) • Newly diagnosed Ph+ ALL in combination with chemotherapy. • As monotherapy in Ph+ ALL for whom no other kinase inhibitors are indicated or T315I-positive Ph+ ALL.
Prednisone Corticosteroid Usually oral Rarely Intravenous (IV)	Approved for the treatment of ALL
Rituximab (Rituxan®) Monoclonal Antibody Intravenous (IV)	Used off-label for treatment of ALL

Drug Name Type of Drug Administration	Indications
Tisagenlecleucel (Kymriah®) Chimeric Antigen Receptor (CAR) T-Cell Therapy Intravenous (IV)	Approved for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse
Vincristine (Oncovin®) Plant Alkaloid Intravenous (IV)	Approved for the treatment of acute leukemia

Pre-Phase Steroid Therapy and Supportive Care. Patients with ALL often start treatment soon after getting diagnosed. Before the start of induction therapy, many people receive steroids. This is known as “pre-phase therapy.” Steroids are very good at getting rid of the leukemia cells, and they often help people feel better fairly quickly.

Pre-phase therapy is made up of a corticosteroid, usually **prednisone** or **dexamethasone**, alone or in combination with another drug such as **vincristine** or **cyclophosphamide**. You may also receive other drugs and hydration to help prevent tumor lysis syndrome (TLS).

For more drug information, see **Table 5** on page 24.

The pre-phase therapy often lasts from 5 to 7 days. During this time, the treatment will reduce the number of leukemia cells in your body. This helps reduce the risk of TLS (for more information on TLS, see page 41). It also gives your doctor time to get the results of important genetic tests that can help plan your treatment.

You may also receive “supportive care”—healthcare that relieves symptoms caused by cancer and by cancer treatment. The goal of supportive care is to improve the patient’s quality of life and to relieve discomfort as much as possible. Supportive care for ALL should be given whenever a person has symptoms that need to be controlled. For patients with ALL, supportive care may include blood transfusions, antibiotics, antiviral drugs, growth factors, pain medications and specialized nursing care, and may be given during any phase of treatment.

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 return to 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**). Based on their risk group, some patients may also receive **cyclophosphamide** or **pegaspargase**.

In addition to chemotherapy, patients may also receive a monoclonal antibody such as **inotuzumab ozogamicin (Besponsa®)**, **ofatumumab (Kesimpta®)** or **rituximab (Rituxan®)**. While these monoclonal antibodies have not been approved by the Food and Drug Administration (FDA) for induction in ALL, they may be prescribed as an off-label treatment. Off-label drug use refers to the practice of prescribing a drug for a different purpose than what the FDA approved. This practice is called “off-label” because the drug is being used in a way not described in its package insert.

About 25 percent of adults with ALL have a subtype called Philadelphia chromosome-positive (Ph+ ALL). For patients with Ph+ ALL, a tyrosine kinase inhibitor (TKI) is often also included. The more commonly used TKIs for Ph+ ALL include **imatinib (Gleevec®)**, **dasatinib (Sprycel®)** or **ponatinib (Iclusig®)**. For more information on Ph+ ALL, see page 33.

Adults who are age 65 and older, or those who have other serious health conditions, may receive the same drugs mentioned above for induction, although the doses of drugs may be reduced and/or the anthracycline may be removed from the regimen.

During induction, patients should also receive treatment to prevent ALL from spreading to the central nervous system (CNS). This is called “CNS-directed treatment.” For more information, see *Central Nervous System (CNS)-Directed Treatment* below.

Typically, the severity of the disease and the side effects of this initial therapy result in a hospital stay of 4 to 6 weeks. During this time, patients receive supportive care until their blood counts recover. This may include transfusions of red blood cells and platelets, antibiotics to prevent and treat infections and growth factors to help improve white blood cell counts. 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.

For more drug information, see **Table 5** on page 24.

Central Nervous System (CNS)-Directed 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, it is crucial to administer therapy directed to the central nervous system; without the routine treatment targeting the central nervous system, leukemia cells can eventually spread there. “CNS prophylaxis” is treatment given to lower the risk of leukemia cells spreading to the CNS.

CNS-directed treatment should be given to all patients throughout the entire course of ALL therapy, from induction through the long-term maintenance phase of treatment.

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 (typically, **hydrocortisone**).
- 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. Cranial radiation is no longer routinely used in the treatment of ALL, except in patients who have leukemia cells in the cerebrospinal fluid at the time of diagnosis or those with CNS relapse. In addition, some regimens for T-cell ALL still use cranial irradiation for CNS prophylaxis, although this is becoming less common.

Radiation therapy is split into a number of treatments called “fractions” that are given each day from Monday to Friday over a period of weeks. The number of days of treatment depends on the dose of radiation required to treat the leukemia cells in the central nervous system.

Assessing Treatment Response. At the end of induction, 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/near normal
- All signs and symptoms of ALL are gone

If you do not achieve a remission after the first course of induction chemotherapy, it may be an indication that the cancer is difficult to treat. In this situation, a second course of induction is usually given. If you do not achieve a remission after two courses of induction, you may be treated with regimens designed for refractory disease. See *Treatments for Relapsed and Refractory ALL* on page 36.

Sometimes, leukemia cells can hide inside the testicles. If you still have evidence of leukemia in the testicles at the end of induction, you may receive radiation therapy to the testicles during the consolidation phase of treatment.

Measurable Residual 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 measurable residual disease (MRD). When a patient tests positive for MRD, it means that residual cancer cells were found. When a patient tests negative, no residual cancer cells were found.

Patients who have achieved remission after initial treatment, but who are MRD-positive, are at increased risk of their disease coming back. Testing for MRD can help doctors identify patients who may benefit from further treatment with intensified therapies such as allogeneic stem cell transplantation.

The tests used most often to detect MRD are flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing. clonoSEQ® is an FDA-cleared test for measuring MRD in ALL patients. These 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 and at subsequent timepoints during the treatment. Recommendations for additional MRD testing depend on the treatment regimen used.

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. The optimal treatment for ALL patients requires additional intensive therapy after remission.

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

Consolidation. The second phase of treatment is called consolidation. This phase, also called "intensification," begins once ALL is in remission. The goal of consolidation is to kill any remaining leukemia cells that could cause a relapse. Consolidation is often based on whether the patient is MRD-positive or MRD-negative after induction. Most treatment plans also call for the continuation of CNS-directed treatment.

For patients who are MRD-positive, **blinatumomab (Blinicyto®)** is often the recommended treatment. Blinatumomab is a liquid administered slowly into a vein by IV as a continuous infusion over a period of 28 days for each cycle. Hospitalization of the patient is typically recommended for the first few days of treatment. Outside the hospital, patients need to carry an infusion device with them.

For most patients who are MRD-negative, consolidation consists of multiagent chemotherapy. 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 is usually given in cycles over 4 to 6 months. Researchers are studying whether patients who are MRD-negative may also benefit from blinatumomab as part of consolidation.

For patients with Ph+ ALL, a tyrosine kinase inhibitor (TKI) is usually continued.

As part of consolidation, some patients in remission may receive a stem cell transplant. Doctors usually recommend stem cell transplantation for patients who are likely to relapse due to high-risk genetic features, or for patients who have high rates of MRD after induction.

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.

Stem Cell Transplantation. For some patients whose disease is in remission and who can tolerate intensive chemotherapy, the doctor may recommend stem cell transplantation during consolidation. The goal of stem cell transplantation is to cure the patient's cancer. The process typically involves administering intensive chemotherapy followed by an infusion of healthy stem 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 the patient completes 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 is not 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 receive a "conditioning therapy" that consists of high doses of chemotherapy, either with or without radiation therapy, to kill the remaining leukemia cells still present in the body. The conditioning therapy is also given to suppress the immune system so that the body does not reject the donor stem cells.

After the conditioning therapy, patients receive donor stem cells by intravenous infusion. Allogeneic transplantation uses healthy blood-forming cells from an

HLA-matched donor. The cells can come from a family member or an unrelated person or from a donated umbilical cord. The donated stem cells restore the bone marrow's ability to form new blood cells.

Ideally, an allogeneic stem cell transplant will generate a new immune system for the patient, one 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 (the "graft") perceive the leukemia cells in the body 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.

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. Doctors can prescribe medications that can try to 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* and *Graft-Versus-Host Disease*. Visit www.LLS.org/TreatmentVideos for videos about stem cell transplantation.

Maintenance. The third phase of treatment is called maintenance. It is the final, and longest, stage of treatment. It usually lasts for about 2 years. The goal of maintenance is to lower the risk of 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.

Most maintenance regimens include:

- **6-mercaptopurine** taken at home by mouth
- **Methotrexate** taken at home by mouth
- **Vincristine** given at a healthcare setting by IV injection
- Corticosteroids (**prednisone** or **dexamethasone**) given at home by mouth

For patients with Ph+ ALL, a tyrosine kinase inhibitor (TKI) is often continued 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 medication as prescribed can increase the chance that the cancer will relapse (return).

For more information about oral drug adherence (taking medicine as prescribed), see the free LLS booklet *Oral Treatment Adherence Facts*.

Special Treatment Considerations

Philadelphia Chromosome-Positive (Ph+) ALL. About 25 percent of adults with ALL have a subtype called Philadelphia chromosome-positive ALL (also known as "Ph+ ALL or "Ph-positive ALL"). It is the most common chromosomal abnormality in patients with B-cell ALL.

The leukemia cells of these patients have the Philadelphia chromosome, which is formed by a translocation (rearrangement) 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.

Tyrosine kinases inhibitors (TKIs) work to block these overactive enzymes and may stop cancer cells from growing. TKIs typically used to treat Ph+ ALL include **dasatinib (Sprycel®)**, **imatinib (Gleevec®)**, or **ponatinib (Iclusig®)**.

Patients who have Ph+ ALL are typically treated with tyrosine kinase inhibitors (TKIs), combined with other medication, either chemotherapy or a steroid. The use of a later generation TKI such as dasatinib and ponatinib typically results in deeper levels of remission and is associated with better long-term survival. Patients also receive CNS-directed therapy during treatment.

Previously, all eligible patients with Ph+ ALL who had entered a remission were recommended to receive an allogeneic stem cell transplant in first complete remission; however, recent clinical trials with the second and third generation TKIs in combination with some of the new immunotherapies (**blinatumomab** or **inotuzumab ozogamicin**) and CNS-directed intrathecal chemotherapy have resulted in excellent responses, suggesting that patients with Ph+ ALL may not require allogeneic transplant for long-term survival. Generally, TKI therapy is recommended to continue indefinitely for patients who do not receive a transplant in first complete remission.

For patients who cannot tolerate intensive chemotherapy, researchers are also studying TKI-based regimens with low-dose chemotherapy or chemotherapy-free treatments with blinatumomab and inotuzumab ozogamicin.

Philadelphia Chromosome-like (Ph-like) ALL. About 10 to 30 percent of adults with ALL 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. Recent studies have analyzed the genetic profile of patients with some subsets of Ph-like ALL and found that using TKIs and other targeted therapies may help treat these types of leukemia. These patients require special attention as Ph-like ALL is more resistant to standard chemotherapy and may require allogeneic transplant in first remission.

T-Cell ALL. T-cell ALL is a type of ALL that starts in early forms of cells that are to become T cells. T-cell ALL makes up about 25 percent of ALL cases in adults.

For adolescents and young adults with T-cell ALL, pediatric, intensive chemotherapy regimens have resulted in improved outcomes. Suitable patients should receive early intensified induction with a regimen of four drugs containing **vincristine**, **pegaspargase**, an anthracycline (such as **daunorubicin** or **doxorubicin**) and a corticosteroid (such as **dexamethasone** or **prednisone**), followed by an intensive consolidation regimen. Recently, the addition of **nelarabine (Arranon®)** to intensive pediatric regimens has been shown to further

improve disease-free survival for children and young adults with T-cell ALL. Patients not suited for a pediatric-intensive regimen should receive multiagent chemotherapy based on the protocol of their treatment center.

For people with relapsed and refractory T-cell ALL, nelarabine is an approved treatment. Proteasome inhibitor **bortezomib (Velcade®)** in combination with chemotherapy is also being studied to reduce the rate of relapse in patients with T-cell ALL. Still, an allogeneic stem cell transplant may be recommended for patients who have a high level of measurable residual disease (MRD) at the end of consolidation therapy. However, the timing of a transplant depends upon whether a donor is available and the patient's health at the time of potential transplant. See page 31 for more information on stem cell transplantation.

Adolescents and Young Adults (AYA). The term “AYA population” generally refers to older adolescents and young adults age 15 to 39 years at diagnosis. Historically, AYAs with ALL experience poorer survival and higher treatment toxicity compared to younger children. During the last decade, however, a new focus on research designed specifically for AYAs has led to improvements in treatment outcomes.

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. CNS-directed therapy is started earlier and given longer. Some children receive longer maintenance therapy than adults.
- Adult protocols use allogeneic stem cell transplantation more often compared to pediatric protocols.

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. Clinical trials continue to study 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”). In other patients, the cancer does not respond to treatment, and there is no remission. 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, so that treatment stops 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.

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

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 where 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

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

- A clinical trial, see page 38 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
- **Bortezomib** + chemotherapy for patients with T-cell ALL
- **Blinatumomab**
- **Inotuzumab ozogamicin**
- 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 (see below), including:
 - **Tisagenlecleucel (Kymriah®)**
 - **Brexucabtagene autoleucel (Tecartus®)**

Chimeric Antigen Receptor (CAR) T-Cell Therapy. CAR T-cell therapy is a type of immunotherapy that uses the patient's own immune cells called "T cells" (white blood cells that help the body fight infections and cancer) to identify 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®)**

For more drug information see **Table 5** on page 24.

For more comprehensive information, see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy*.

Visit www.LLS.org/TreatmentVideos for videos about CAR T-cell therapy.

Talk to your doctor about:

- Therapies under study in clinical trials for refractory or relapsed 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 pediatric and adult 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.

See the free LLS booklet *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 has features of two forms of leukemia: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), or sometimes a combination of T-cell and B-cell ALL. 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, and 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 genetic abnormalities found in patients with MPAL. Some studies have shown that ALL therapy may be the preferred approach. Currently there is no standard therapy for MPAL, but clinical trials are underway.

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, sometimes in combination with a tyrosine kinase inhibitor (TKI). This is sometimes followed by allogeneic stem cell transplantation.

For patients with a Philadelphia chromosome-negative (Ph-) subtype of MPAL, treatment often consists of an ALL-induction regimen followed by allogeneic stem cell transplantation. For patients for whom an ALL regimen does not result in remission, treatment can be switched to an AML-like regimen followed by consolidation therapy with an allogeneic stem cell transplant.

Visit www.LLS.org/CTSC to work with Clinical Trial Nurse Navigators to search for clinical trials for people diagnosed with MPAL.

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 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. Pain medications and physical therapy are often effective treatments for 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 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 these distressing side effects.

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 Effect 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 booklet *Navigating Life During and After a Blood Cancer Diagnosis* available in adult and young adult versions.**

Talk to your doctor about:

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

Financial Concerns

Paying for healthcare is a major concern for many people who are living with leukemia. The high cost of cancer treatment can lead to significant financial and emotional stress for both patients and their families. Even if you have health insurance, cancer can still take a toll on your finances. You may have new expenses such as co-payments or travel for treatment. You may also have less income if you need to take time off from work.

Speak with your healthcare team if you have any concerns about being able to afford your treatment. They may be able to provide information and resources that can help. Health insurance plans may not cover all of the costs of cancer care, but there are many resources available for prescription drug payment. In addition, several major drug manufacturers currently provide patient assistance or prescription assistance programs. These programs can provide both insured and uninsured patients free or reduced-cost medications.

LLS offers financial assistance programs to help with insurance premiums, treatment-related co-payments, travel and other expenses for eligible patients. Other organizations also offer financial assistance programs. You can call an LLS Information Specialist at (800) 955-4572 for more information about our financial assistance programs.

For more information and resources to help cope with the financial costs of cancer care, please see the free LLS booklet *Cancer and Your Finances*.

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 6** below).

Table 6. 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 5 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 <i>BCR-ABL1</i> gene is recommended.		

Adapted from National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia 2024.

People 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 stopping smoking, protecting skin 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* available in adult and young adult versions.

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 have a complete remission after treatment, 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 5-year overall survival rates of approximately 20 percent to 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

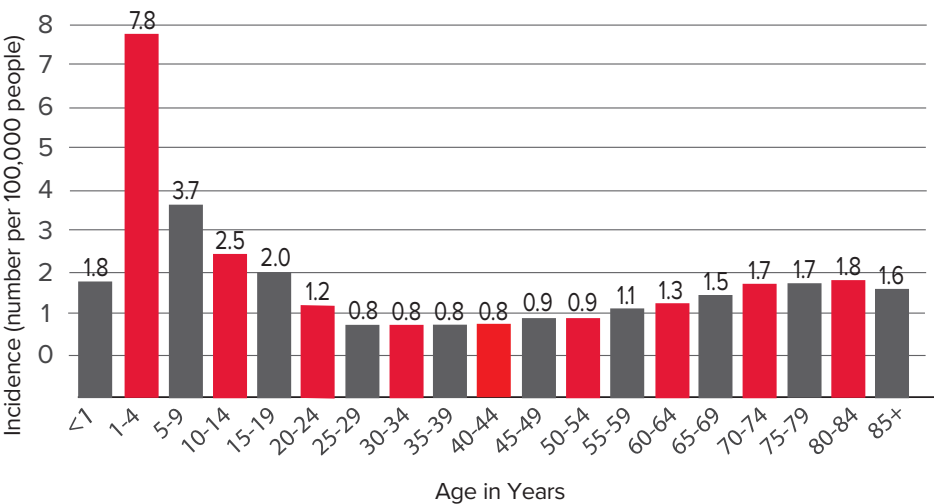
being studied in clinical trials. As a result, the outlook may be better for people diagnosed with ALL today.

Incidence, Causes and Risk Factors

Incidence. Approximately 6,540 new cases of acute lymphoblastic leukemia (ALL) were expected to be diagnosed in the United States in 2023. In 2019, there were an estimated 81,689 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 (see **Figure 5**).

Figure 5. Age-Specific Incidence Rates for Acute Lymphocytic Leukemia (All Races), 2015-2019



The horizontal axis shows 4-year age intervals. The vertical axis shows the frequency of new cases of ALL each year per 100,000 people, by age group. Source: SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2023 February 18]. 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 age 70, are at greater risk of developing ALL.
- Sex. Males are more likely than females to develop ALL.
- Race/ethnicity. In the United States, ALL is more common in Hispanics and whites.

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.

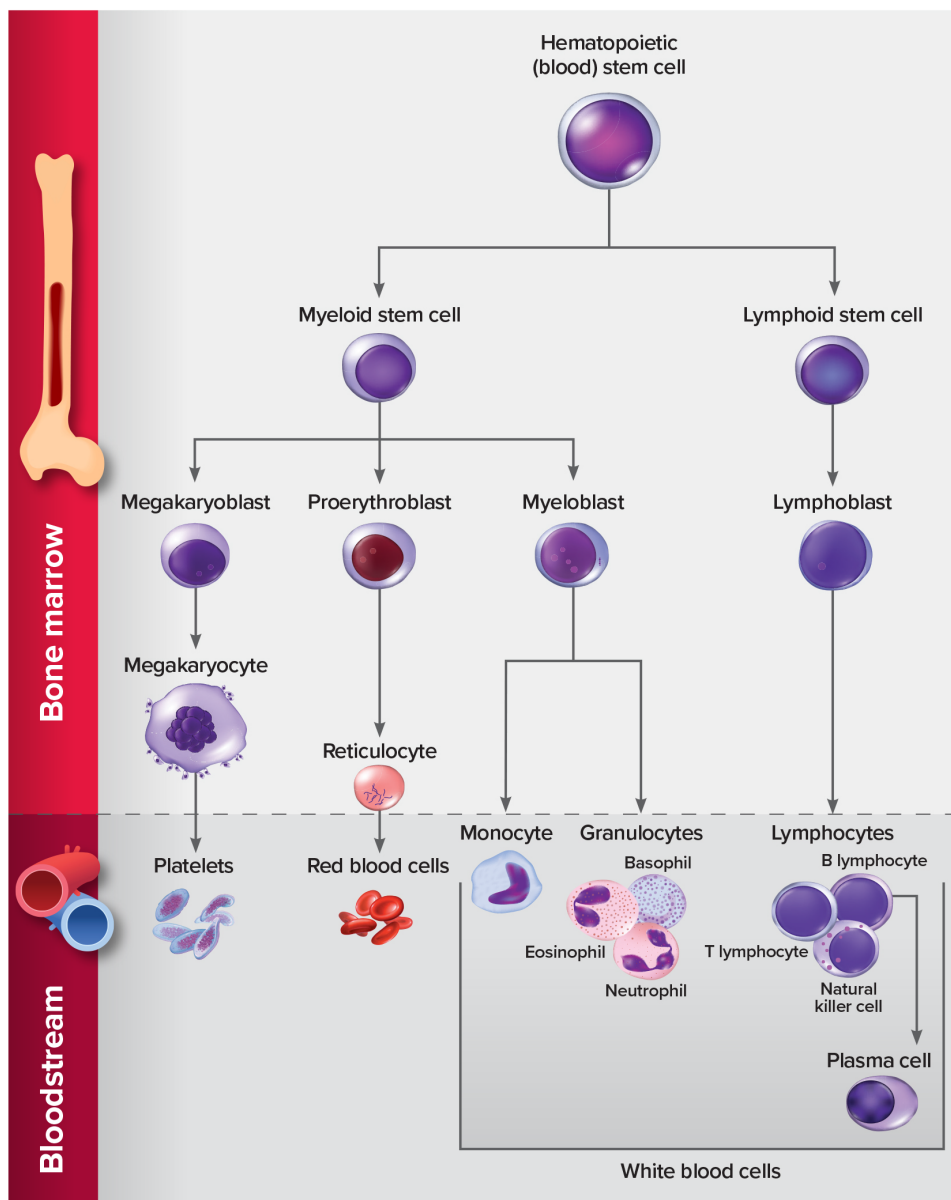
Plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals each have a special role. They include:

- 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 B12
- 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 6** on page 49). The blood cells are suspended in the plasma.

Figure 6. Blood Cell and Lymphocyte Development

Most blood cells start as hematopoietic (blood) stem cells in the bone marrow. Hematopoietic stem cells are the most immature blood-forming cells. They must mature (go through many stages) to become a red blood cell, white blood cell or platelet. Some blood cells mature in the bone marrow. Other blood cells leave the bone marrow and travel to other parts of the body to develop into mature blood cells.



Stem cells in the bone marrow develop into three types of mature blood cells:

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 (CO₂) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO₂ 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)

Bone Marrow. 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 can also be collected from the placentas and the umbilical cords of newborn infants. The cells are stored and later used for transplantation.

The Lymphatic System

The lymphatic system is the tissues and organs that produce, store and carry lymphocytes (a type of white blood cell) that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). See **Figure 7** on page 52.

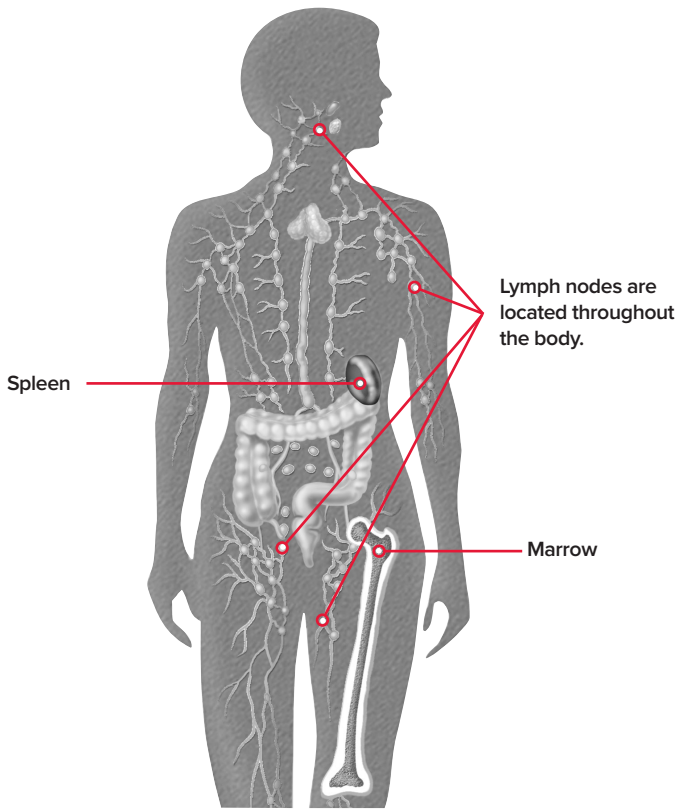
The bone marrow is really two organs in one. It is (1) the organ that forms blood cells, and it is (2) the organ that forms lymphocytes, which make up part of the immune system.

The bone marrow produces 3 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.

Figure 7. The Lymphatic System



The lymphatic system is part of the immune system. The normal immune system helps to protect the body from infection. The marrow, lymph nodes and spleen are parts of the immune system. There are about 600 lymph nodes throughout the body.

Lymph nodes and other lymphoid tissues that are commonly involved in lymphoma are those around the ears and jaw, in the tonsils and adenoids, in the front and back of the neck, above and below the collarbone, in the armpit, near the elbow, in the chest, in the abdomen, in the pelvis and in the groin. The spleen contains many clusters of lymphocytes that can become malignant and grow, leading to the enlargement of the spleen. The gut-associated (intestinal) lymph tissue may also be the site of lymphoma development.

Resources and Information

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

For Help and Information

Consult with an Information Specialist. Information Specialists can assist you through cancer treatment, financial and social challenges and give accurate, up-to-date disease, treatment and support information. Our Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials (Research Studies). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Nutrition Consultations. Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients of all cancer types and their caregivers. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit www.LLS.org/nutrition for more information.

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

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

Financial Assistance. LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

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

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 to access exclusive content, submit ideas and topics, and connect with other listeners.

3D Models. LLS offers interactive 3D images to help visualize and better understand blood cell development, intrathecal therapy, leukemia, lymphoma, myeloma, MDS, MPNs and lab and imaging tests. Visit www.LLS.org/3D for more.

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. Visit www.LLS.org/SuggestedReading to find out more.

Connecting with Patients, Caregivers and Community Resources

LLS Community. 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. Visit www.LLS.org/community to join.

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

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

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

Advocacy and Public Policy. Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit www.LLS.org/advocacy for more information.

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. For more information, please visit www.LLS.org/ResourceDirectory to view the directory.

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

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 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. For more information, please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

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 Health Program. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get 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 and those who lived, worked or were in school in that 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. Seek medical advice 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

Allogeneic Stem Cell Transplantation. A treatment that replaces a person's damaged or diseased bone marrow with healthy blood-forming stem cells from a donor. **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 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 Nervous System (CNS). The brain and the spinal cord.

Central Nervous System (CNS)-Directed Therapy. 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. Drug 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*.

Chromosome. Part of a cell that contains genes in a linear order. Human cells have 23 pairs of chromosomes, for 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).

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.

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 material found inside cells that carries 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.

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.

First-Line Therapy. The first treatment given for a disease.

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.

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, a type of white blood cell, to treat low white blood cell counts.

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.

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 fewer 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. A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer and other diseases. Some types of immunotherapy include monoclonal antibody therapy and CAR T-cell therapy.

Induction. The first phase of treatment that is given to reduce quickly and significantly the number of leukemia cells in the body.

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.

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

Intravenous Injection. Injection into a vein.

Karyotype. An organized profile, or picture, 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.

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

Lymphatic System. The tissues and organs that produce, store and carry white blood cells that fight infections and other diseases. This system includes the lymph nodes, spleen, bone marrow, tonsils and thymus.

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.

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, *Measurable Residual Disease*.**

Minimal Residual Disease. See Measurable Residual Disease (MRD).

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.

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.

Oral Therapy. Treatment that is taken by mouth.

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

Phagocyte. A type of white blood cell that protects the body from infection by eating and killing microorganisms, 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.

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 to 1 million 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.

Prophylaxis. An attempt to prevent 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.

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

Subcutaneous Injection. An injection in which the needle goes under the skin into the space between the skin and muscle, but it does not enter the muscle.

Supportive Care. Care given to improve the quality of life of people who have a disease by preventing or treating the symptoms of the disease and the side effects caused by treatment of the disease.

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*.**

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.

References

- Abou Dalle I, Jabbour E, Short NJ. Evaluation and management of measurable residual disease in acute lymphoblastic leukemia. *Therapeutic Advances in Hematology*. 2020;11: 2040620720910023. Published March 6, 2020.
- Alaggia R, Amador C, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720-1748.
- Berry DA, Zhous S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncology*. 2017;3(7):e170580.
- Foà R, Chiaretti S. Philadelphia chromosome-positive acute lymphoblastic leukemia. *New England Journal of Medicine*. 2022;386(25):2399-2411. doi: 10.1056/NEJMra2113347. PMID: 35731654.
- George BS, Yohannan B, Gonzalez A, et al. Mixed-phenotype acute leukemia: clinical diagnosis and therapeutic strategies. *Biomedicines*. 2022;15;10(8).
- Jabbour, E, Short, NJ, Jain, N. et al. The evolution of acute lymphoblastic leukemia research and therapy at MD Anderson over four decades. *Journal of Hematology & Oncology*. 2023; 16(22). <https://doi.org/10.1186/s13045-023-01409-5>.
- Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood*. 2017;129(5);572-581. doi:10.1182/blood-2016-07-726588.
- Kunz T, Hauswirth AW, Hetzenauer G, et al. Changing landscape in the treatment of adult acute lymphoblastic leukemia (ALL). *Cancers (Basel)*. 2022;14(17):4290.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute lymphoblastic leukemia. Version 4.2023–February 5, 2024. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed March 1, 2024.
- Paul S, Kantarjian H, Jabbour EJ. Adult acute lymphoblastic leukemia. *Mayo Clinic Proceedings*. 2016;91(11):1645-1646. doi:10.1016/j.mayocp.2016.09.010.
- Short NJ, Kantarjian H, Jabbour E. Optimizing the treatment of acute lymphoblastic leukemia in younger and older adults: new drugs and evolving paradigms. *Leukemia*. 2021;35(11):3044-3058.
- Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer Journal*. 2017;7(6):e577. doi:10.1038/bcj.2017.53.

[illegible]

[illegible]

NOTES

This image shows a single page of white paper with horizontal ruling lines. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.

Get support.
Reach out to our
Information Specialists.



The Leukemia & Lymphoma Society® team consists of highly trained oncology social workers and nurses who are available by phone, email and live chat Monday through Friday, 9 a.m. to 9 p.m. (ET).

- Get one-on-one personalized support and information about blood cancers
- Know the questions to ask your doctor
- Discuss financial resources
- Receive individualized clinical-trial searches
- Get connected to resources

Contact us at
800.955.4572
or **www.LLS.org/**
InformationSpecialists

(Language interpreters
can be requested.)



For more information, please
contact our Information Specialists
800.955.4572 (Language interpreters
available upon request).

National Office 3 International Drive, Suite 200 Rye Brook, NY 10573

The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families. Find out more at www.LLS.org.