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Acute Lymphoblastic Leukemia (ALL) in Children and Teens



First Edition 2021

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ONCOLOGY

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

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



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

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

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Introduction

This booklet provides information about acute lymphoblastic leukemia (ALL) in children and also includes information about ALL in young adults. Acute lymphoblastic leukemia is also known as “acute lymphocytic leukemia” and “acute lymphoid leukemia.”

People of any age can develop ALL, but most cases are diagnosed in children. It is the most common childhood cancer in the United States. An average of 2,761 children and young adults younger than 20 years of age were diagnosed with leukemia each year from 2012 to 2016 in the United States.¹

Over the past several decades, the cure rates and survival outcomes for children with ALL have improved dramatically. Childhood ALL now has one of the highest cure rates of all childhood cancers. Today, most young patients diagnosed with ALL can expect to have full and productive lives after treatment. Many survivors return to school, attend college, enter the workforce, marry and become parents.

However, more work remains to be done. New therapies are being studied in clinical trials to find cures for all children who have ALL, including those with high-risk disease and those who relapse after treatment.

This booklet provides medical information about ALL as well as advice to help you, your child and your family cope. 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.

Visit www.LLS.org/booklets to view, download or order all free LLS publications mentioned in this booklet.

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¹ Source: *Facts 2019-2020*. The Leukemia & Lymphoma Society. April 2020.

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Leukemia

Leukemia is a cancer of the blood and bone marrow. Bone marrow is the sponge-like tissue in the center of most bones, where blood cells form. Leukemia begins in one of the immature stem cells in the bone marrow. One or more changes

(mutations) occur in the DNA of the cell, and it becomes a type of cancer cell, called a “leukemia cell.”

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

The four major types of leukemia are:

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

Disease progression (meaning how quickly the disease gets worse) is one of the factors that doctors consider when classifying leukemia. Leukemias can be “acute” or “chronic.” Acute leukemias develop and progress rapidly and typically get worse quickly if they are not treated. Chronic leukemias usually progress more slowly. Acute leukemias are much more common in children than chronic leukemias.

Leukemia is also classified by the type of blood cell that becomes cancerous. Blood stem cells develop into two primary types: lymphoid and myeloid. As lymphoid stem cells mature, they become a type of white blood cell called a “lymphocyte.” The two major types of lymphocytes are B cells and T cells. Myeloid stem cells eventually become red blood cells, platelets or other types of white blood cells (other than lymphocytes). Leukemia is called “lymphocytic” or “lymphoblastic” if the cancerous change begins in a lymphoid cell. Leukemia is called “myeloid” or “myelogenous” if the cancerous cell change starts in an early form of a myeloid cell.

This booklet focuses on ALL, but there are other cancers, called “lymphomas,” that also begin in lymphoid cells. Most lymphomas arise from more mature lymphoid cells, but in rare instances they can develop from lymphoblasts. The main difference between lymphoblastic leukemias and lymphoblastic lymphomas is the location of the cancer cells. Leukemias, such as ALL and CLL, generally affect the bone marrow and blood. In contrast, lymphomas are mostly located in lymph nodes or other lymphatic tissues or organs. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy. Therefore, if you have been diagnosed with lymphoblastic lymphoma, this book may also be helpful for you.

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

Acute Lymphoblastic Leukemia

How Acute Lymphoblastic Leukemia (ALL) Develops. 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 clumping together (clotting) at the site of an injury.

Blood cells begin as hematopoietic stem cells in the bone marrow. Hematopoietic stem cells are immature (undeveloped) blood cells. In healthy bone marrow, these blood-forming cells eventually develop into red blood cells, white blood cells and platelets in a process called “differentiation.”

In people with ALL, a mutation or a series of mutations in the DNA (genetic material) of the lymphoid stem cell result in the formation of leukemia cells (lymphoblasts), which are immature cells stuck in the earliest stage of cell development. These leukemia cells, also referred to as “ALL blasts” or “ALL cells,” cannot mature into fully functioning lymphocytes which are white blood cells that help fight infection.

Genetic errors in a mutated cell cause the cell to keep growing and dividing, whereas a healthy cell would stop dividing and eventually die. Every cell that arises from the initial leukemia blast cell also has its 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 leukemic blast cells that cannot fight infections and too few mature, functional red blood cells, white blood cells and platelets.

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

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

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. A pediatric hematologist-oncologist specializes in the care of children with blood disorders and blood cancers.

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. Your child's blood counts may show a high number of white blood cells, but if your child has ALL, these cells are not fully developed and do not fight infection well. In ALL, the leukemia cells begin to reproduce very quickly and compete with the other healthy blood cells for nutrients and space. Consequently, children with ALL may not have enough mature red blood cells, white blood cells and/or platelets, and often have symptoms related to low blood cell counts.

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

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

Symptoms of a low white blood count (leukopenia) include:

- Frequent infections
- Recurrent fevers

Symptoms of a low platelet count (thrombocytopenia) include:

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

Symptoms may also be related to leukemia cells collecting in other parts of the body. These symptoms may include:

- Unexplained weight loss or loss of appetite
- Pain in bones and joints
- Swollen lymph nodes
- Enlarged spleen or liver
- Abdominal pain
- Wheezing, coughing or painful breathing

The symptoms listed above are common symptoms of ALL, but do not include all possible symptoms, as children may experience symptoms differently. It is also important to note that the symptoms of ALL may be similar to those of other blood disorders or medical conditions. Speak with your doctor if your child has any of the above symptoms to ensure proper diagnosis and treatment.

Diagnostic Testing

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

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

Talk to your doctor about

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

Some of the tests may be repeated both during and after treatment to evaluate if treatment is working.

Medical History. Your child's doctor will take a thorough medical history. The doctor will ask about any health problems or treatments that your child has had. The history may include information about past illnesses, injuries, other treatments and medications. Some illnesses run in families, so the doctor may also ask about the health of your child's blood relatives.

Physical Examination. The doctor will want to know about your child's current symptoms and will conduct a physical examination. During the examination, the doctor may listen to your child's lungs and heart and carefully examine the body for signs of infection and disease. To check the internal organs, the doctor may also feel different parts of your child's body. For example, the doctor may feel the abdomen to see if your child has an enlarged liver or spleen. Because ALL can cause enlarged lymph nodes, the doctor may check your child's lymph nodes in the neck and armpits. In boys, the doctor may also examine the testicles to see if there are any masses.

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

Children with ALL often have a high number of white blood cells, but most of these are leukemia cells that do not protect against infection. Meanwhile, they may not have enough mature white blood cells, red blood cells or platelets.

Even if the CBC findings suggest leukemia, an ALL diagnosis is usually only made after examination of a sample of bone marrow cells.

Bone Marrow Aspiration and Biopsy. These are two procedures that remove bone marrow cells and test them for abnormalities. They are generally done at the same time, either at the doctor's office or in a hospital. Most children are under sedation or general anesthesia during these procedures.

The samples are usually taken from the patient's pelvis (hip bone). Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special hollow biopsy needle is inserted through the hip bone and into the bone marrow to remove (aspirate) a liquid sample of bone marrow cells. For a bone marrow biopsy, a wider needle is used to remove a sample of solid bone that contains bone marrow. Both samples are sent to the lab where they are examined under a microscope. See **Figure 1** on page 8.

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

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

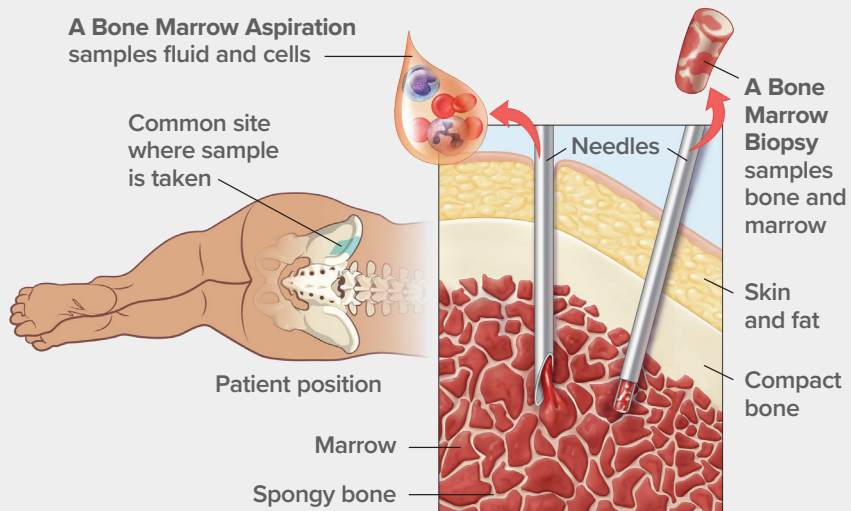
Bone Marrow Aspiration. A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

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

Both bone marrow tests are done with special needles. Adults and older teens may be given a local anesthetic and be "awake" during this procedure, but most children are under sedation or given general anesthesia, which makes them "sleep" briefly during the tests. The sample of cells is usually taken from the patient's hip bone.

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

Bone Marrow Aspiration and Biopsy



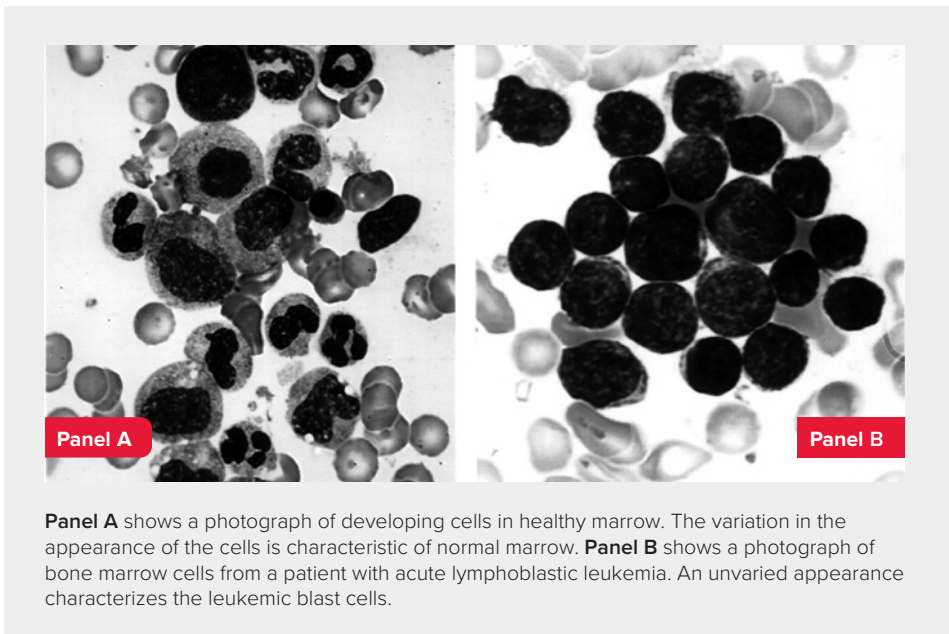
Left: The place on the back of the patient's pelvic bone where a bone marrow aspiration or biopsy is done. **Right:** Where the needle goes inside the bone to collect the liquid sample for aspiration and the bone sample for biopsy. The needles are different sizes for each of these tests.

Cell Assessment. At the lab, a hematopathologist examines the blood and bone marrow samples. A hematopathologist is a doctor who has special training in identifying blood diseases by studying cells under a microscope.

The hematopathologist examines the blood and bone marrow cells under a microscope to determine their size, shape and type, as well as to identify other cell features. Whether the cells look like normal, mature blood cells or abnormal, immature blood cells (blast cells) is an important finding. See **Figure 2** below.

The percentage of blast cells identified in the samples is another important finding. Typically, there are no blast cells in the blood, and no more than 5 percent of the cells in the bone marrow are blast cells. Generally, a diagnosis of ALL in children requires a finding of 25 percent or more of the cells in the bone marrow to be lymphoblasts.

Figure 2. Acute Lymphoblastic Leukemia (ALL) Cells



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

Flow Cytometry. This laboratory test can detect specific types of cancer cells based on the antigens or proteins on the surface of the cells. The pattern of the surface proteins is called the “immunophenotype.” It is used to help diagnose specific types of leukemia and lymphoma cells.

A bone marrow sample is often used for this test, but it can also be done with a blood sample. The sample of cells is treated with special antibodies created in a laboratory that only bind to cells that have a specific antigen on them.

Depending on the type of leukemia, the leukemia cells can have different antigens on their surfaces. Certain antigens, called “cluster of differentiation (CD) proteins,” are helpful in identifying leukemia cells.

Flow cytometry helps to confirm an ALL diagnosis. It is also used to determine the type of lymphocytes (B cells or T cells) in which the disease originated and to assess the maturity of the cells. In addition, flow cytometry is used to check treatment results.

Genetic Tests. The following tests are used to examine the chromosomes and genes in a patient’s leukemia cells.

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

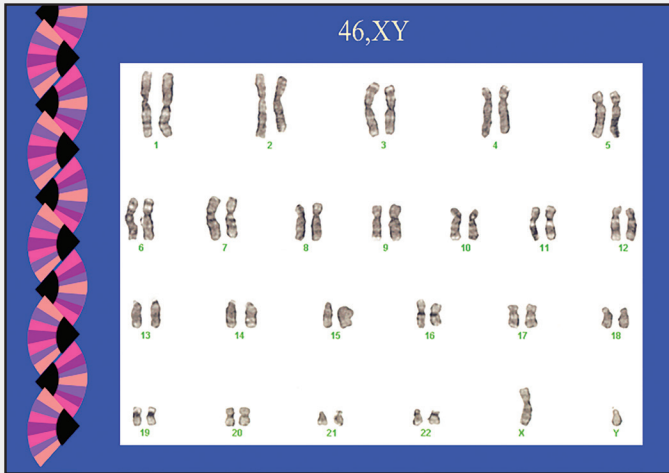
Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure. In many cases of ALL, the chromosomes of leukemia cells have abnormal changes that can be seen under a microscope. These changes include translocations and/or extra chromosomes. A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. Sometimes pieces from two different chromosomes break off and trade places. This results in a “fusion gene,” an abnormal gene formed when two different genes fuse together.

Cytogenetic testing can be done with 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 prior to examination. The stained sample is examined under a microscope and photographed to show the arrangement of the chromosomes (called a karyotype). The karyotype shows if there are any abnormal changes in the size, shape, structure or number of chromosomes in the leukemia cells. See **Figure 3** on page 11.

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 pages 27, 34, 38.

Fluorescence in Situ Hybridization (FISH). This lab test is used to identify and examine specific genes or chromosome regions in cells. In cases of ALL, doctors use FISH to detect certain abnormal changes in the genes and chromosomes within leukemia cells, including translocations. Pieces of DNA that contain special fluorescent dyes are made in the laboratory and added to the leukemia cells on a glass slide. When the pieces of DNA bind to specific genes or areas of chromosomes on the slide, they light up when viewed under a fluorescence microscope. Many abnormal changes can be seen with a standard microscope,

Figure 3. Normal Male Karyotype



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

but FISH testing can also detect changes that are too small to be seen in more basic cytogenetic tests.

Molecular Genetic Analysis. Polymerase chain reaction (PCR) is a very sensitive laboratory technique that is used to detect and measure certain genetic mutations and chromosomal changes that are too small to be seen with a microscope. Different types of PCR testing can essentially increase (amplify) 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 500,000 to 1,000,000 normal cells. PCR testing is one method used to determine the amount of minimal residual disease (MRD), the small amount of cancer cells that may remain in the body after treatment. This test can be done with either a bone marrow sample or a blood sample.

“Next-generation sequencing” is a catch-all term used to describe a number of different modern genetic sequencing technologies. These technologies allow for DNA and RNA sequencing and are capable of detecting very small gene fusions and translocations within leukemia cells that cannot be detected by routine cytogenetic tests or FISH.

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

Diagnosis and Cell Classification

In children, a diagnosis of ALL generally requires a finding that 25 percent or more of the cells in the bone marrow are leukemic blasts of lymphoid origin (lymphoblasts). The ALL subtype is determined based on a patient's lab test results.

Subtypes of ALL. The subtypes of ALL are identified based on certain features of the leukemia cells. Determining the ALL subtype is an important factor in treatment planning. The doctor will discuss with you which drug combinations and “protocols” are indicated based on your child's ALL subtype. In medicine, protocols are detailed plans of treatments and procedures. The doctor may also talk about whether a clinical trial may be an appropriate treatment option.

Immunophenotyping. Leukemia cells can be classified by the antigens, known as “immunophenotypes,” found on their surfaces. The World Health Organization (WHO) classifies ALL based on the immunophenotype of the leukemia cell in the following ways (see **Table 1** on page 13):

- B-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into B cells. In children, if the bone marrow has 25 percent or more lymphoblasts, the disease is called B-cell lymphoblastic leukemia (B-cell ALL). If the lymphoblasts are restricted to a mass in a lymph node or other lymph tissue and less than 25 percent of the bone marrow cells are lymphoblasts, it is called B-cell lymphoblastic lymphoma. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy.

B-cell ALL is the most common ALL subtype, accounting for approximately 80 percent of cases among children with ALL. Within the B-cell lineage, the cell surface markers (proteins) differ according to the stage of cell maturation.

Before 2008, the WHO classified B-cell lymphoblastic leukemia as “precursor B-lymphoblastic leukemia.” This older term is sometimes used to distinguish B-cell ALL from mature B-cell ALL. Mature B-cell ALL is now referred to as “Burkitt leukemia.” The treatment for Burkitt leukemia is based on therapy for non-Hodgkin lymphoma and is very different than the treatment used for ALL.

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

- T-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into T cells. If the bone marrow has 25 percent or more lymphoblasts, the disease is called T-cell lymphoblastic leukemia (T-cell ALL). If the bone marrow has less than 25 percent lymphoblasts and the lymph nodes are enlarged, it is called T-cell lymphoblastic lymphoma. This subtype is less common than B-cell ALL and occurs more often in adults than in children. T-cell ALL accounts for approximately 15 to 20 percent of ALL cases in children.

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

B-cell lymphoblastic leukemia/lymphoma

B-cell lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)

B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

B-cell lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*

B-cell lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged

B-cell lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*

B-cell lymphoblastic leukemia/lymphoma with hyperdiploidy

B-cell lymphoblastic leukemia/lymphoma with hypodiploidy

B-cell lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*

B-cell lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*

Provisional entity: B-cell lymphoblastic leukemia/lymphoma, BCR-ABL1–like

Provisional entity: B-cell lymphoblastic leukemia/lymphoma with iAMP21

T-cell lymphoblastic leukemia/lymphoma

Provisional entity: early T-cell precursor lymphoblastic leukemia

Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma

Source: Classification of acute lymphoblastic leukemia types created by the World Health Organization (WHO).

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

Genetic Changes. In addition to classifying ALL as either B-cell or T-cell, it can be further classified based on changes to certain chromosomes and genes (see **Tables 2 and 3** on pages 14-16). This identification of specific genetic abnormalities is critical for disease evaluation, risk stratification and treatment planning.

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

Another type of genetic change associated with ALL is a translocation. In a translocation, the DNA from one chromosome breaks off and becomes attached to a different chromosome.

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

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

Table 2. Common Genetic Alterations in Childhood B-Cell ALL

Genetic Subtype	Common Alterations	Frequency in ALL	Prognosis
Abnormalities in chromosome number			
High hyperdiploidy (51-67 chromosomes)		25%	Favorable
Low hyperdiploidy (47-50 chromosomes)		14%	Previously unfavorable, now intermediate
Hypodiploidy (<44 chromosomes)	Near-haploidy (24-31 chromosomes), low-hypodiploidy (32-39 chromosomes)	1-2%	Unfavorable
Recurrent chromosomal translocations			
t(12;21)(p13;q22)	<i>ETV6-RUNX1 (TEL-AML1)</i>	20%	Favorable
t(1;19)(q23;p13·1)	<i>TCF3-PBX1 (E2A-PBX1)</i>	4%	Intermediate
t(17;19)(q22;p13)	<i>TCF3-HLF</i>	<0.5%	Unfavorable

Table 2 (continued).

Genetic Subtype	Common Alterations	Frequency in ALL	Prognosis
<i>KMT2A</i> (<i>MLL</i>) rearrangements		5-6%	Unfavorable (infants), Intermediate (non-infants)
t(1;11)(q21;q23)	<i>KMT2A-MLLT11</i>		Less favorable
t(4;11)(q21;q23)	<i>KMT2A-AFF1</i> (<i>AF4</i>)		Particularly unfavorable
t(9;11)(p22;q23)	<i>KMT2A-MLLT3</i> (<i>AF9</i>)		
t(10;11)(p12;q23)	<i>KMT2A-MLLT10</i> (<i>AF10</i>)		
t(11;19)(q23;p13.3)	<i>KMT2A-MLLT1</i> (<i>ENL</i>)		
Other fusion partners			
t(9;22)(q34;p11.2)	<i>BCR-ABL1</i>	3-5%	Unfavorable prior to TKI therapy; Intermediate with TKI therapy?
Other			
Ph-like	<i>IGH-CRLF2</i> , <i>P2RY8-CRLF2</i>	7-8%	Unfavorable
	<i>ABL1</i> , <i>ABL2</i> , <i>CSF1R</i> , <i>PDGFRB</i> rearrangements	5-6%	Unfavorable
	<i>EPOR</i> , <i>JAK2</i> rearrangements	2%	Unfavorable
Trisomy 21-associated ALL	<i>P2RY8-CRLF2</i> , <i>JAK2</i> mutations	50-60% of DS-ALL	Intermediate
iAMP21	Multiple copies of <i>RUNX1</i>	2%	Unfavorable
<i>DUX4</i> rearrangements	<i>IGH-DUX4</i> , <i>ERG-DUX4</i>	3-7%	Favorable
<i>MEF2D</i> rearrangements	<i>MEF2D-BCL9</i> , <i>MEF2D-HNRNPUL1</i>	3-6%	Unfavorable
<i>ZNF384</i> rearrangements	<i>EP300-ZNF384</i>	4%	Intermediate

Note that percentages may total more than 100% due to co-occurrence of genetic lesions.

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; DS-ALL, Down syndrome-associated ALL; iAMP21, intrachromosomal amplification of chromosome 21; TKI, tyrosine kinase inhibitor; t, translocation between chromosomes; q, the long arm of a chromosome (the lower half); p, the short arm of a chromosome (the upper half).

Adapted from Tasian SK, Hunger SP. Genomic characterization of paediatric acute lymphoblastic leukaemia. *British Journal of Haematology*. 2017;176:867-882.

Table 3. Common Genetic Alterations in Childhood T-Cell ALL

Genetic Subtype	Common Alterations	Frequency of T-cell ALL	Prognosis
Recurrent chromosomal translocations			
t(10;14)(q24;q11)	<i>TLX1 (HOX11)</i> fusions	5-10%	Favorable
t(7;19)(q34;p13)	<i>LYL1</i> fusions	10%	Unfavorable
t(1;14)(p32;q11), t(1;7)(p32;q34), t(11;14)(p15;q11), t(11;14)(p13;q11)	<i>TAL1, LMO1, LMO2</i> fusions	50-60%	Unfavorable
t(11;14)(p15;q11), t(5;14)(q35;q32)	<i>TLX3 (HOX11L2)</i> fusions	20-25%	Unfavorable (some studies), Intermediate (some studies), Favorable (some studies)
t(8;14)(q24;q11)	<i>TRA-MYC, TRC-MYC</i>	1%	Probably unfavorable
7p15 translocations	<i>HOXA10, HOXA9</i> overexpression	3%	Unfavorable
<i>KMT2A</i> (11q23) rearrangements	<i>KMT2A-AFF1, KMT2A-MLLT1</i>	5%	Possibly favorable
t(10;11)(p13;q21)	<i>PICALM-MLLT10 (CALM-AF10)</i>	5-10%	Unfavorable (some studies), Intermediate (other studies)
t(9;14)(q34;q32)	<i>NUP214-ABL1</i>	5-15%	Unfavorable (some studies), Intermediate (other studies)
<i>NOTCH1</i> mutations		50-60%	Favorable
ETP		10-15%	Unfavorable (some studies), Intermediate (other studies)
<i>FBXW7</i> mutation		15%	
Other T-ALL		6%	

Note that percentages may total more than 100% due to co-occurrence of genetic lesions.

Abbreviations: T-ALL, T cell-acute lymphoblastic leukemia; ETP, early thymic precursor or early T-cell precursor; t, translocation between chromosomes; q, the long arm of a chromosome (the lower half); p, the short arm of a chromosome (the upper half).

Adapted from Tasian SK, Hunger SP. Genomic characterization of paediatric acute lymphoblastic leukaemia. *British Journal of Haematology*. 2017;176:867-882.

Learning About Your Child's Diagnosis. You are likely to experience a wide range of emotions from the time your child is diagnosed with cancer as well as during and after treatment. These emotions may include shock, denial, fear, anger, guilt and sadness. You may feel that life for your child and family will never be the same. Allow yourself to feel sad. Understand that you are not to blame for your child's diagnosis.

Over time, you and your family will find ways to adapt and gradually develop a new sense of normalcy. All of these feelings are to be expected, but if you feel consumed by negative feelings and emotions or are unable to function, seek professional help. Psychologists, social workers and spiritual advisers may also help you come to terms with your child's diagnosis. It is important to work through your feelings so you can help your child cope and you can continue to manage other aspects of family life and work.

Talking to Your Child About His or Her Diagnosis. Regardless of age, children are usually aware when their health causes their parents concern. Your child may experience a variety of emotions, such as anger, guilt, fear, anxiety and sadness, possibly all in quick succession.

Sometimes parents wish to shield their child from information about the illness and its treatment. Keep in mind that children will use their imagination to fill in perceived gaps of information. Sharing information about the illness and treatment helps your child build trust in both you and the members of the treatment team, so that he or she feels comfortable talking about fears and concerns. Encourage your child to talk about his or her concerns and ask questions.

Introduce your child to treatment team members who can provide psychosocial support. These include psychologists, social workers, art or play therapists and child-life specialists. In addition to helping you explain the illness and its treatment to your child, they can help your child better understand his or her disease through play or other activities.

Keep the discussion age appropriate when you talk to your child about his or her diagnosis. Consider the following guidelines, organized by age:

Baby/Toddler (0 to 3 Years)

- Children this young do not have an understanding of illness or cancer. However, they are aware of changes to routines and the feelings of people around them.
- Children in this age-group may be afraid of the medical staff and medical procedures.
- Babies and toddlers may be afraid of abandonment or being left at the hospital. Offer physical and verbal reassurance.

Preschool/Kindergarten (4 to 6 Years)

- Children may have some understanding of an illness, such as a cold, but may not grasp the implications of a serious illness.
- Children’s primary focus will be the symptoms they are experiencing in any specific moment.
- Children in this age-group may be afraid of pain, so explain tests or treatments to them in advance.
- Assure your child that he or she did nothing wrong to cause the cancer.

Elementary/Middle School (7 to 12 Years)

- Children in this age-group may have a better understanding of serious illness, but not specifically cancer.
- They may have heard things about cancer at school, from friends, on TV, or they may have found information online. Ask your child what he or she knows and correct any misunderstandings, especially those that cause distress.
- Explain tests, treatments, and other medical procedures in advance. Your child may be afraid of pain and resist some tests or procedures. Be honest. If a procedure may be painful, work with the healthcare team and decide how to explain what will be done to lessen pain and why the procedure is important.
- Talk to your child in advance about possible changes to his or her physical appearance.
- You may need to discuss fertility preservation with your child. Some cancer treatments can affect fertility. Fertility preservation, such as egg or sperm banking, may be an option for children who have begun puberty. Fertility preservation needs to be done before treatment begins. Enlist members of the healthcare team to help with this sensitive discussion.
- You may see signs of regression in a child’s behavior, such as thumb sucking, bed-wetting or tantrums.
- A child may use play to process the information—play-acting doctor/patient scenarios, for example.
- If the cancer treatment will result in any changes to the child’s daily routine, explain the changes ahead of time so that the child will know what to expect.

High Schoolers/Teenagers (13 to 18 Years)

- Teenagers understand more about cancer and may want to know more. You may still need to correct any misinformation your teenager has heard about cancer from school, friends, TV and movies, or has found online.
- Teenagers may want to participate in decisions about their treatment. Include them in discussions with members of the healthcare team, as appropriate.
- You may need to discuss fertility preservation with teenagers. Some cancer treatments can affect fertility. Fertility preservation, such as egg or sperm banking, needs to be done before treatment begins. Enlist members of the healthcare team to help with this sensitive discussion.
- High schoolers and teenagers may also be very concerned about changes to their physical appearance, such as hair loss and losing or gaining weight, as well as worrying about how their peers will react to the changes.
- As teenagers struggle to find independence, a cancer diagnosis may feel like a setback that can lead to feelings of frustration and anger. They may try to test their boundaries or engage in risky behaviors, such as drinking, drug use, or sex.

Ways to Help Your Child Cope. It will help your child cope with his or her diagnosis if you:

- Provide structure to increase your child's sense of control. Children crave structure in their environment. Make things as consistent as possible. For example, plan a regular routine that you will follow during your time together in the hospital or clinic.
- Acknowledge and praise your child when he or she is doing difficult things. Intermittent praise is the best way to reinforce the desirable behaviors that you want to see in your child.
- Use the same consequences for unacceptable or inappropriate behavior as you did before your child was diagnosed with cancer. Consistency will maintain structure and normalcy.
- Show that you respect your child's anger, worry, sadness or fear. Give your child appropriate outlets for expressing these feelings, such as drawing or keeping a journal.
- Keep your child busy with activities during treatment to take his or her mind off difficult and unpleasant experiences.

- Help your child stay connected with friends from home and school with phone calls, emails, or visits, if possible.
- Ask for professional assistance for your child if he or she is having an especially difficult time adjusting to the cancer diagnosis and its treatment.

Siblings. When a child is diagnosed with cancer, everyone in his or her family is affected by the experience, including the child's brothers and sisters. Siblings can feel angry, anxious, lonely, sad, guilty, or even resentful of the new attention their sibling receives. You can help your other children cope with a sibling's diagnosis in some of the following ways:

- Give them the chance to talk about how the experience is affecting them.
- Be open and willing to answer questions about their brother or sister's cancer and treatment.
- Reassure younger siblings that they cannot "catch" cancer from their brother or sister. Explain that their brother or sister did not do anything that caused the cancer.
- Warn siblings that their brother or sister who has cancer may have less energy or lose his or her hair.
- Explain that other concerned family members and friends may ask them about their sibling's diagnosis. Talk about appropriate responses.
- Remember that brothers and sisters still have their own problems, unrelated to their sibling's cancer. Their problems are real and require your attention.
- Provide consistent, fair discipline to all your children, even though it may be more difficult right now.
- Let all your children know that you love them and are proud of them.

Siblings need to continue to go to school and participate in their usual activities, as much as possible. Ask friends, family, other parents and teachers for help. However, disruptions to routines are inevitable, and siblings may feel lost or overlooked. Arrange for regular "alone time" with each child.

Make sure the school is aware of the diagnosis. Talk to your other children's teachers. Ask your hospital's social worker or psychologist, or your school psychologist, whether your community offers any programs for siblings of children who have cancer. For additional assistance finding programs for siblings, you can also call an LLS Information Specialist at (800) 955-4572.

SuperSibs, a program of Alex's Lemonade Stand Foundation, provides programs and support for the siblings of children with cancer. Visit www.alexslimonade.org/supersibs to learn more.

For additional support and information, please call an Information Specialist or visit www.LLS.org/FamilyWorkbook to find information for caregivers.

Treatment Planning

Choosing a Hospital and Doctor for Your Child’s Cancer Treatment. Once you learn that your child has ALL, you need to decide where to go for treatment. Most children with cancer receive treatment at hospitals that specialize in treating children with cancer. The doctors and other healthcare providers at these centers have special training and expertise in giving comprehensive care to children. These centers are often members of the Children’s Oncology Group (COG). This is the world’s largest organization devoted to clinical research to improve the care and treatment of children with cancer.

Going to a specialized children’s cancer hospital helps ensure that your child gets the best available treatment. You can ask your child’s pediatrician or family doctor for a referral, or you can call an LLS Information Specialist at (800) 955-4572 to find hospitals that specialize in treating children with ALL.

Most children with ALL are cared for by a pediatric hematologist-oncologist. A pediatric doctor (pediatrician) specializes in the treatment of children. A hematologist is a doctor who has special training in disorders of the blood, and an oncologist is a doctor who has special training in cancer. A pediatric hematologist-oncologist specializes in blood cancers in children.

Children who are diagnosed with ALL usually need to start treatment as soon as possible after diagnosis. Some families may wish to seek a second opinion, particularly if their child has a high-risk subtype of ALL or if the ALL has come back (relapsed) after initial treatment. A second opinion may help you feel more confident about your child’s treatment plan. The second opinion should come from a pediatric hematologist-oncologist, preferably one who specializes in childhood ALL. This doctor will usually have the most knowledge and experience regarding the latest treatment options.

If you are unsure or feel uncomfortable about how to tell your child’s doctor you are getting a second opinion, call our Information Specialists to discuss a way that makes you comfortable. You may also want to check with your insurance company to be sure that a second opinion will be covered.

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

Blood Tests. Doctors test blood to help plan treatment. Below are some 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 the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

Blood Chemistry Profile. This blood test measures the levels of certain substances released into the blood by organs and tissues in the body. These substances include electrolytes (such as sodium, potassium and chloride), fats, proteins, glucose (blood sugar), uric acid and enzymes. Blood chemistry test findings indicate how well a person's kidneys, liver and other organs are working. Although this test is not used to diagnose leukemia, if the results show that there is an abnormal amount of a particular substance in the blood, it may be a sign of disease or some other health problem. A blood chemistry profile also provides helpful information about any potential organ damage caused by leukemia cells or ALL treatments.

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

Coagulation Tests. These tests measure the blood's ability to clot and stop bleeding. Certain proteins, called "coagulation factors," are needed for clotting. These proteins are made by the liver. In addition to checking how well the blood is able to clot, these tests can determine whether there are deficiencies in some proteins, such as the protein called fibrinogen. Coagulation tests can help assess your child's risk for excessive bleeding.

Tumor Lysis Syndrome (TLS) Panel. Children 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 the toxic substances all at once. The effects of TLS can be life threatening; they can be severe during the early phases of treatment, especially if white blood cell counts are very high before induction therapy. A TLS panel can help the doctor assess if your child is likely to get or already has TLS.

HLA Typing. This consists of a blood test to identify certain proteins, called human leukocyte antigens (HLAs), found on the surface of most cells in the body. These proteins make up a person's tissue type, which varies from person to person. They also play an important role in the body's immune response to

foreign substances by helping the body distinguish its own cells from foreign cells. HLA typing is done before allogeneic stem cell transplantation to find out if there is a tissue match between the donor and the person receiving the transplant. Although HLA typing is not used to diagnose leukemia, it is an important test for newly diagnosed ALL patients, if allogeneic stem cell transplantation is being considered as a treatment option. For more information on stem cell transplantation, see page 36.

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

The procedure used to collect the cerebrospinal fluid from the spinal column is 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 bones (vertebrae) and into the cerebrospinal fluid. 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.

Imaging Tests. These tests create pictures (images) 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 a 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 the 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 sugar more quickly than normal cells. A PET scan may be done to see if there are cancer cells in the lymph nodes or organs.

Positron Emission Tomography-Computed Tomography (PET-CT) Scan.

This procedure combines images from both a PET scan and a CT scan. The combined scans give a more detailed image of areas inside the body than either scan can give by itself.

Magnetic Resonance Imaging (MRI) Scan. This imaging test uses magnetic fields and radio waves to create images of the body's organs and tissue, 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 leukemia cells in a boy's testicles. If the testicles are not the same size or have any lumps, the doctor may order an ultrasound to see whether there is a mass in the testicles.

Echocardiogram. A computerized image of the heart is created by bouncing ultrasound waves off internal tissues or organs in the chest. An echocardiogram shows the size, shape and position of the heart, as well as its internal structures. It also shows if the heart is beating and pumping blood normally. Since 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 pumps blood.

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

Prognostic Factors. Certain factors can affect a patient's prognosis—the likely outcome of a disease or ailment. Doctors use prognostic factors to help predict how a patient's disease is likely to respond to treatment. These factors help doctors plan the most appropriate treatment regimen for each patient.

Prognostic factors for children with B-cell ALL include:

- Age: The leukemia cells in infants younger than 1 year and children older than 10 years tend to be more resistant to treatment. Stronger treatments may be needed to kill the leukemia cells.
- White blood cell count: Children with white blood cell counts of $50 \times 10^9/L$ or greater at the time of diagnosis need stronger treatment.
- Genetic factors: Certain changes in the chromosomes or genes can make the leukemia cells either easier or harder to treat. See **Table 2** on pages 14-15, and **Table 3** on page 16.
- Central nervous system involvement: Children with ALL who have leukemia cells in the central nervous system at diagnosis are at a higher risk of disease relapse.
- Treatment response: Children who have a better response to the initial induction therapy have a lower risk of disease relapse.

For children with T-cell ALL, risk stratification is primarily based on their early treatment response. Children who have a better response to the initial induction therapy have a lower risk of disease relapse.

Risk Groups for B-cell ALL. Your doctor may describe your child's ALL in terms of its risk group. Patients are assigned to a risk group based on age, genetic and clinical features of the disease and the results of laboratory tests.

Knowing your child's risk group helps the doctors develop the most effective treatment plan for your child. Patients with lower-risk ALL are more likely to have a favorable outcome and need less aggressive treatment. Children in the high-risk and very high-risk groups usually receive more intense treatment than children in the lower-risk groups.

Standard (Low) Risk: Children older than age 1 and younger than age 10; low white blood cell count; favorable response to treatment.

High Risk: Children older than 10 years; high white blood count at the time of diagnosis; children with unfavorable genetic changes; children with minimal residual disease, a very small amount of leukemia cells still detectable by sensitive lab tests after 4 weeks of induction therapy.

Very High Risk: Children younger than age 1; children with certain genetic changes; children who have a slow response to initial treatment and signs of leukemia after the first 4 weeks of treatment; children with minimal residual disease after four weeks of induction therapy.

Fertility. Some cancer treatments can affect your child's fertility (the ability to have children in the future). Before your child begins treatment, it is important to talk with the doctor about whether the treatment could affect your child's fertility. You may also 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 child's fertility.

Delaying treatment to address fertility options may not always be recommended. Many children with ALL need to start treatment right away. Nevertheless, before treatment begins, it is important to talk with your child's doctor about the effect treatment may have on fertility.

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

Treatment Options

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

Many children with leukemia have treatment options including standard treatment or a clinical trial. It is important to talk to your child's doctor about the best treatment option for your child.

Typically, treatment for children with ALL consists of a multi-drug regimen that is divided into five phases: induction, consolidation, interim maintenance, delayed intensification and maintenance. High-risk patients may have additional phases of treatment. Most treatment regimens take 2 to 3 years to complete.

The main treatment for ALL is chemotherapy. Some treatment plans may also include targeted agents and stem cell transplantation. Treatment regimens for ALL include central nervous system (CNS) prophylaxis to prevent leukemia cells from spreading to the area around the brain and spinal cord. CNS prophylaxis is typically given to children throughout all phases of ALL treatment. For more information about CNS prophylaxis, see page 27.

Talk to your doctor about

- Your child's treatment options and the results you can expect from treatment
- The results you can expect from standard treatment
- The possibility of your child participating in a clinical trial

Induction Therapy. The first phase of chemotherapy is called "induction therapy." The goal of induction therapy is to destroy as many cancer cells as possible in order to achieve (induce) a remission. Remission means that leukemia cells are no longer found in bone marrow samples and blood counts have returned to normal.

Induction therapy lasts for 4 weeks. The specific drugs, dosages and timing of administration depend on several factors, including the patient's age, the specific features of the leukemia and the overall health of the patient. See **Table 4**, on page 30.

Your child may spend some or most of this time in the hospital during this phase of treatment, depending on your child's clinical condition. For some children, the hospital stay is the first time they have been away from home for an extended period of time. Most hospitals allow a parent to stay at the child's bedside during hospitalization.

Providing age-appropriate information about the illness and its treatment will help your child build trust in you and the members of the treatment team. Talking with your child about his or her fears and concerns will also help your child feel more comfortable.

For practical guidance about how to support your child and other family members, deal with your own concerns, share the news with extended family and friends, and make the transition to life after treatment, visit www.LLS.org/FamilyWorkbook for the *Caring for Kids and Adolescents with Blood Cancer* workbook.

Children with standard-risk ALL often receive three drugs for the first month of treatment. These include the chemotherapy drugs **vincristine** and **pegaspargase** and the corticosteroid **dexamethasone**. For children in the high-risk groups, another chemotherapy drug in the anthracycline family, such as **daunorubicin** or **doxorubicin**, is typically added. Older children may receive the corticosteroid **prednisone** instead of dexamethasone.

In addition to the treatment(s) above, children with Philadelphia chromosome-positive (Ph+) ALL and Philadelphia chromosome-like (Ph-like) ALL are also given a tyrosine kinase inhibitor (TKI) medication, such as **imatinib (Gleevec®)** or **dasatinib (Sprycel®)**. Some children with Ph-like ALL may be treated with a TKI called **ruxolitinib (Jakafi®)**, usually in a clinical trial. See page 38 for more information on special treatment considerations for children with Ph+ ALL and Ph-like ALL.

Central Nervous System (CNS) Prophylaxis. Pediatric regimens typically include treatment to prevent the spread of leukemia cells to the central nervous system and to kill any leukemia cells that may already be present in the brain and spinal cord. It is uncommon for leukemia cells to be present in the cerebrospinal fluid at the time of diagnosis, occurring in only 3 to 7 percent of cases. However, without the routine administration of a therapy targeting the central nervous system (referred to as “CNS prophylaxis”), leukemia cells will eventually spread to the cerebrospinal fluid in a large percentage of patients (50 percent or more). The CNS-directed therapy is typically given to all patients throughout the entire course of ALL treatment. It begins during the induction phase and continues throughout the rest of the treatment regimen.

Central nervous system-directed therapy may include:

- **Intrathecal chemotherapy**, in which anti-cancer drugs are injected into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord. The most common intrathecal chemotherapy drug used in children with ALL is **methotrexate**. Sometimes, other drugs such as **cytarabine** and a corticosteroid are used, particularly in children with high-risk ALL.

- **High-dose systemic chemotherapy**, in which anti-cancer drugs are injected into a vein and travel through the blood to cells throughout the body. **High-dose methotrexate** is the most common drug used for this treatment in children with high-risk B-cell ALL.
- **Cranial irradiation**, in which radiation therapy to the brain is used to kill cancer cells. Cranial radiation is no longer routinely used in children with ALL, except in those with leukemia cells in their cerebrospinal fluid at the time of diagnosis or those with CNS relapse. Cranial radiation is almost never used in very young children. Radiation therapy can increase a child's risk of developing long-term and late effects, such as problems with thinking, growth and development. However, it is very effective in the treatment of CNS leukemia, when indicated.

Assessing Treatment Response. At the end of the month of induction therapy, your child will have another bone marrow aspiration performed. The bone marrow sample is examined under a microscope. (Children with acute lymphoblastic lymphoma may not need a bone marrow test and may instead require imaging studies only; see page 12 for information about acute lymphoblastic lymphoma.) These tests or imaging studies are to check whether your child's leukemia or lymphoma is in complete remission. A complete remission is achieved when:

- No leukemic blast cells are detected in the bone marrow (with a microscope)
- No more than 5 percent of cells in the bone marrow are blast cells
- No blast cells are in the bloodstream
- Blood cell counts are back to normal
- All signs and symptoms of ALL are gone

Over 95 percent of children achieve a remission at the end of induction therapy. However, remission does not mean that your child is cured. Your child still needs more treatment to ensure that the disease does not come back (relapse).

Even when a complete remission is achieved, some leukemia cells that cannot be seen with a microscope may remain in the body. The presence of these cells is referred to as minimal/measurable residual disease (MRD). Patients who have achieved remission after initial treatment but have MRD are at increased risk of disease relapse. Testing for MRD can help your child's doctor re-evaluate your child's ALL risk category and determine whether your child may benefit from further intensified therapies.

It is important for your child to get tested for MRD even after achieving remission. There are very sensitive tests to detect MRD. The most widely used tests are flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing. These tests use samples of bone marrow cells.

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

If your child tests negative for MRD, that indicates that the tests did not detect residual leukemia cells. If your child tests positive for MRD, there are still detectable leukemia cells inside the bone marrow. Children who are MRD-positive after induction therapy are categorized as having high-risk or very high-risk ALL. Depending on the amount of MRD, your child's doctor may change the treatment plan. Your child may undergo more intense treatment, or the doctor may recommend a stem cell transplant.

If your child is in remission but tests positive for MRD, the doctor may prescribe a drug called **blinatumomab (Blinicyto®)**. Blinatumomab is approved by the US Food and Drug Administration (FDA) to treat adults and children with:

- B-cell ALL and are in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- Relapsed or refractory B-cell ALL.

For patients who do not achieve remission after the first course of induction chemotherapy, a second course of chemotherapy is given, usually using different chemotherapy drugs.

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

Table 4. Some Drugs Used for Treatment and/or in Clinical Trials for ALL

Anthracyclines

- Daunorubicin (Cerubidine®)
- Doxorubicin (Adriamycin®)
- Mitoxantrone (Novantrone®)
- Idarubicin (Idamycin®)

DNA-Repair Enzyme Inhibitor

- Etoposide (VP-16; VePesid®; Etopophos®)

DNA-Damaging Agents

- Cyclophosphamide (Cytoxan®)
- Ifosfamide (Ifex®)

Enzymes That Prevent Cells From Surviving

- Asparaginase *Erwinia chrysanthemi* (Erwinaze®)
- Calaspargase pegol-mknl (Asparlas™)
- Pegaspargase (PEG-L asparaginase; Oncaspar®)

Tyrosine Kinase Inhibitors

- Imatinib mesylate (Gleevec®)
- Dasatinib (Sprycel®)
- Nilotinib (Tasigna®)
- Bosutinib (Bosulif®)
- Ponatinib (Iclusig®)

Antimetabolites

- Clofarabine (Clolar®)

Antimetabolites (continued)

- Cytarabine (cytosine arabinoside, Ara-C; Cytosar-U®; DepoCyt®)
- Fludarabine (Fludara®)
- Hydroxyurea (Hydrea®)
- 6-mercaptopurine (Purinethol®; Purixan®)
- Methotrexate (Xatmep®; Abitrexate®; Trexall®)
- Nelarabine (Arranon®)
- 6-thioguanine (thioguanine; Tabloid®)

Drugs That Prevent Cells From Dividing

- Vincristine (Oncovin®)
- Vincristine sulfate liposome (Marqibo®)

Synthetic Hormones (Corticosteroids)

- Prednisone
- Methylprednisolone
- Dexamethasone

Immunotherapies

- Blinatumomab (Blincyto®)
- Inotuzumab ozogamicin (Besponsa®)
- Tisagenlecleucel (Kymriah®)
- Rituximab (Rituxan®)

This table includes drugs used for treatment and drugs being studied in clinical trials for the treatment of ALL.

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

Postremission Therapy. “Postremission therapy” refers to treatments given to patients after their disease is in complete remission. Even when MRD test results are negative, undetectable residual cancer cells are believed to remain in the body. Because of this, patients with ALL require additional treatment after they achieve remission. Most of these phases are given in an outpatient setting, while some phases require a brief hospitalization for chemotherapy administration. During this period, children also continue to receive CNS prophylaxis therapy.

Consolidation Therapy. Consolidation (intensification) therapy begins after induction therapy. Higher doses of chemotherapy are typically used during the consolidation phase than those used during the induction phase. The goal of consolidation therapy is to kill any remaining leukemia cells in the body that may cause a relapse. In this phase of treatment, lower-risk patients typically receive less intensive therapy, while higher-risk patients receive therapy that is more intense.

The consolidation phase usually lasts for a period of 4 to 8 weeks, depending on the ALL risk category and treatment protocol. Consolidation chemotherapy does not usually require a hospital stay. It is often given in an outpatient setting, allowing your child to go home after each scheduled treatment. But if there are complications, such as fever or infection, a child may be admitted to the hospital.

The combination of drugs and the duration of therapy for consolidation regimens vary, but can consist of combinations of drugs similar to those drugs used during the induction phase. Generally, several chemotherapy drugs are combined to help prevent the leukemia cells from developing drug resistance.

Some of the drugs frequently incorporated into consolidation regimens include:

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

Interim Maintenance. After consolidation therapy, there is a recovery period called “interim maintenance.” Interim maintenance is typically given for up to 8 weeks, depending on your child’s treatment plan. This phase aims to maintain the remission, but also allows the bone marrow to recover from the effects of therapy. Interim maintenance typically involves non-myelosuppressive chemotherapy (chemotherapy that does not cause decreased blood cell counts). Patients receive **methotrexate** in combination with other chemotherapy agents. Methotrexate is given intravenously. If lower doses are prescribed, it may be given in a clinic. Higher doses may require a 2-3 day stay in the hospital.

Delayed Intensification. The goal of the delayed intensification phase of treatment is to eliminate residual, drug-resistant leukemia cells from the body. It typically lasts 8 weeks and includes chemotherapy combinations similar to those used in the induction and consolidation phases. The exact timing of the doses and the specific drugs given will depend on the individual characteristics of your child’s disease. Some of the drugs that are frequently incorporated into delayed intensification regimens include:

- **Vincristine**
- **Dexamethasone**
- **Pegaspargase**
- **Doxorubicin**
- **6-mercaptopurine**
- **Cyclophosphamide**
- **Cytarabine**

Delayed intensification does not usually require a hospital stay, but children are sometimes admitted to the hospital for complications, such as fever and infection.

Maintenance. Maintenance is the last and longest phase of treatment. The goal of maintenance therapy is to prevent disease relapse. Children receive lower doses of chemotherapy during the maintenance phase and, as a result, tend to have less-severe side effects. Maintenance therapy usually lasts 2 to 3 years. Most maintenance regimens include:

- **Oral 6-mercaptopurine** (administered daily) by mouth
- **Oral methotrexate** (administered weekly) by mouth
- Periodic doses of **vincristine** and corticosteroids (**prednisone, dexamethasone**)
- Intrathecal chemotherapy (to the spinal canal to prevent/treat CNS)

Because some of these medications are taken orally, at home, it is extremely important that a parent or caretaker ensure that the child takes the medication as prescribed by the doctor. Not taking the medication as prescribed by the doctor can increase the chance that the cancer will come back.

Types of Treatment. Not every child with ALL receives the same treatment. Your child’s doctor will tailor your child’s treatment based on the ALL subtype and other factors, such as age, health and how the cancer responds to treatment. In addition to chemotherapy, your child’s treatment may include targeted therapy, immunotherapy or stem cell transplantation. These treatments are discussed in further detail in the following sections.

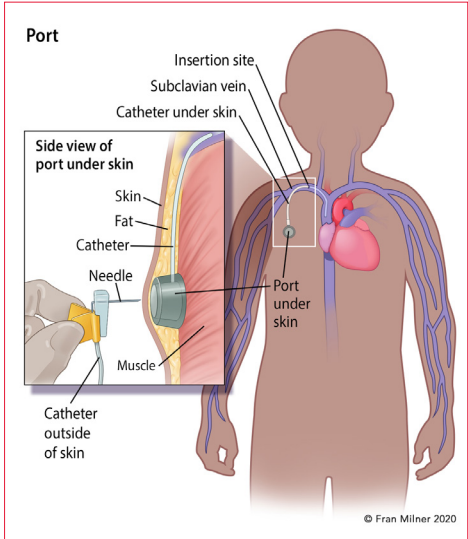
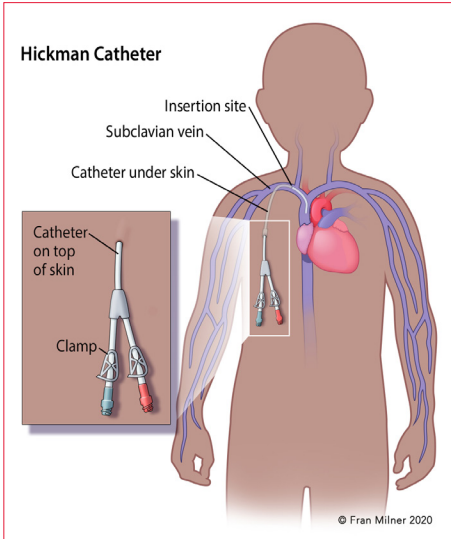
Chemotherapy. The current standard treatment for ALL is long-term chemotherapy. It typically lasts for about 2 to 3 years and it is often intense, especially in the first few months of treatment. The most common treatment regimens use a combination of more than one anticancer drug.

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

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

Some chemotherapy drugs are injected into a vein. During an intravenous (IV) infusion, the drugs are injected slowly over the course of a few hours, or several days in the case of a “continuous infusion.” Often, IV chemotherapy is given through a thin, soft tube called a “central venous line,” a “catheter,” or a “central line.” The central line is usually attached to a “port” that is surgically placed under the skin into the patient’s upper chest, to allow access to the central line. The port and central line can stay in place for months. See **Figure 4** on page 34.

Figure 4. Methods of Intravenous (IV) Injection: Hickman® Catheter and Port



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

Port: A port used with a central line.

Targeted Therapy. Targeted therapy uses drugs or other substances that target and attack specific cancer cells, but are less likely to harm normal cells.

Tyrosine Kinase Inhibitors (TKIs). Tyrosine kinases are enzymes that are a part of many cell functions including cell signaling, growth and division. These enzymes may become too active in patients with an ALL subtype called Philadelphia chromosome-positive ALL (Ph+ ALL). The leukemia cells of these patients have the Philadelphia chromosome, which is formed by a translocation between parts of chromosome 9 and chromosome 22. This chromosomal alteration creates a gene called *BCR-ABL1*, which overproduces tyrosine kinase and thereby causes leukemia cells to grow and divide uncontrollably. For more on Ph+ ALL, see page 38.

Tyrosine kinase inhibitors (TKIs) work to block these overactive enzymes and may stop cancer cells from growing. TKIs are pills taken by mouth. They are generally not used alone to treat ALL. Instead, they are added to a combination chemotherapy regimen.

The following TKIs have been approved to treat Ph+ ALL in children:

- **Imatinib (Gleevec®)**, taken by mouth, is approved for pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy.
- **Dasatinib (Sprycel®)**, taken by mouth, is approved for children age 1 year and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

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

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

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

- **Blinatumomab (Blincyto®)** is a "bispecific" antibody, a type of antibody that can bind to two different antigens at the same time. Blinatumomab is used to treat adults and children with:
 - B-cell ALL in first or second complete remission with minimal disease (MRD) greater than 0.1%
 - Relapsed or refractory B-cell ALL

Blinatumomab is a liquid administered slowly through a vein by IV as a continuous infusion over a period of 28 days. Hospitalization is typically recommended for the first few days of treatment. Side effects of blinatumomab may include:

- Fever
 - Headache
 - Infection
 - Nausea
 - Diarrhea
 - Swelling
 - Neurological complications such as seizures, confusion, disorientation, slurred speech and loss of balance
- **Inotuzumab ozogamicin (Besponsa®)** is a monoclonal antibody linked to a chemotherapy drug. However, it is only indicated for the treatment of adult patients with relapsed or refractory B-cell ALL. Pediatric experience with

inotuzumab ozogamicin is limited, and researchers continue to study this treatment in children. Inotuzumab ozogamicin targets CD22, a cell surface antigen expressed on the cancer cells of most B-cell ALL patients. When inotuzumab ozogamicin binds to the CD22 antigen on B cells, it enters the cell and then releases the chemotherapy drug **calicheamicin**, causing the cell to die.

Chimeric Antigen Receptor (CAR) T-Cell Therapy. CAR T-cell therapy is a type of immunotherapy in which a patient's T cells (a type of white blood cell) are changed in the laboratory so that they will attack cancer cells.

- **Tisagenlecleucel (Kymriah®)** is an FDA-approved for the treatment of patients up to age 25 years who have B-cell ALL that is refractory or in second or later relapse. This treatment is designed to help the body's own immune system fight cancer. Each dose is made for a specific patient, using the patient's own T cells (white blood cells that help the body fight infections and cancer). The T cells are collected from the patient and then genetically modified to add a new gene containing a CAR protein, so that the T cells can identify and kill leukemia cells with CD19 on their surface. These modified cells are infused back into the patient's bloodstream to kill the cancer cells.

While CAR T-cell therapy can be an effective treatment, it is also associated with a relatively high rate of serious complications. As a result, it can only be given at specialized centers that have expertise in delivering this type of treatment.

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

Stem Cell Transplantation. Some patients with ALL may benefit from stem cell transplantation. The goal of stem cell transplantation is to cure the patient's cancer by destroying the cancer cells in the bone marrow with high doses of chemotherapy. Such high doses of chemotherapy, however, can damage the stem cells in the bone marrow, resulting in life-threatening anemia, infections and uncontrolled bleeding. Stem cell transplantation allows doctors to give higher doses of chemotherapy than can typically be given. After the chemotherapy, the patient receives an infusion of healthy stem cells to replace those destroyed by the intensive therapy. The healthy blood stem cells then grow and multiply, forming new bone marrow and blood cells.

There are two main types of stem cell transplantation:

- **Allogeneic**— A patient receives stem cells from a matched or a partially matched donor, either related or unrelated to the patient.
- **Autologous**— A patient's own stem cells are removed before chemotherapy, stored and then returned to the patient's own bloodstream after chemotherapy.

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

Allogeneic Stem Cell Transplantation. Allogeneic stem cell transplantation, which uses donor stem cells, is the most common type of stem cell transplantation used to treat ALL. In preparation for the transplant, patients are given strong doses of chemotherapy, with or without radiation therapy, to kill the remaining leukemic cells in their bodies. This part of the treatment, called “myeloablative conditioning therapy,” also kills cells in the bone marrow including healthy blood-forming cells. After the conditioning therapy, patients receive infusions of the donor stem cells. The donated stem cells restore the bone marrow’s ability to form new blood cells.

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

Unfortunately, sometimes a very serious side effect, called graft-versus-host disease (GVHD), can develop after transplantation of the stem cells. GVHD 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 commonly damaged by GVHD include the skin, liver, stomach, intestines and eyes. GVHD can develop within weeks after transplantation or much later. A doctor can prescribe medications to help prevent or minimize the complications of GVHD.

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

Autologous transplantation is not commonly used to treat patients with 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 your child.

For further information about all types of stem cell transplantation, see the free LLS booklets *Blood and Marrow Stem Cell Transplantation* and *Cord Blood Stem Cell Transplantation*.

Special Treatment Considerations

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL).

About 2 to 4 percent of children with ALL have a subtype called Philadelphia chromosome-positive ALL (also known as “Ph+ ALL” or “Ph-positive ALL”). The leukemia cells of these patients have the Philadelphia chromosome, which is formed by a translocation between parts of chromosomes 9 and 22. A piece of chromosome 9 breaks off and attaches to chromosome 22, and a piece of chromosome 22 similarly breaks off and attaches to chromosome 9. The new, abnormal chromosome 22 is known as the Philadelphia chromosome. This chromosomal alteration creates a gene called *BCR-ABL1*. This gene produces a protein called a tyrosine kinase, which causes the leukemia cells to grow and divide out of control.

Patients who have Ph+ ALL are typically treated with tyrosine kinase inhibitors (TKIs) combined with chemotherapy. This combination has become the standard of care for Ph+ ALL patients. New combinations of drugs for the treatment of Ph+ ALL are also being studied in clinical trials. See *Tyrosine Kinase Inhibitors* on pages 34-35 for more information about TKIs.

Philadelphia Chromosome-like (Ph-like) ALL. About 15 percent of children with ALL have a subtype of B-cell ALL called “Ph-like ALL.” This is a high-risk subtype of ALL in children that seems to peak in adolescents and young adults and is more likely to be seen in males and patients with Down syndrome. It is associated with an unfavorable prognosis.

Ph-like ALL has genetic features similar to 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 be 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 that analyzed the genetic profile of patients with Ph-like ALL have suggested that using TKIs and other targeted therapies may help treat these leukemias. This is an area of active clinical research.

T-cell ALL. This is an aggressive cancer that has historically been associated with a poor prognosis. However, the development of intensive treatment regimens focused on T-cell ALL has led to significant improvements for children with this type of the disease. Treatment outcomes for children with T-cell ALL are now nearly equivalent to those of children with B-cell ALL.

Early intensification of therapy improves outcomes in patients with T-cell ALL. Patients typically receive early intensified induction therapy 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.

Nelarabine (Arranon®) has been approved for the treatment of patients with T-cell ALL and T-cell lymphoblastic lymphoma in adult and pediatric patients age 1 year and older whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Researchers are evaluating the use of nelarabine as a frontline therapy in the consolidation phase of treatment.

Most children with T-cell ALL do not need a stem cell transplant to be cured. Still, a transplant may be recommended for children who have a high level of minimal residual disease (MRD) at the end of consolidation therapy.

Infant ALL. Infant ALL generally refers to cases of ALL diagnosed in children younger than age 1. Leukemia is very rare in infants. There are only approximately 90 cases of infant ALL per year in the United States.

Lower survival rates and poorer outcomes are seen in infants with ALL than in older children with the disease. Most infants with ALL present with aggressive features, including high white blood cell counts, central nervous system involvement and presence of leukemia cells in the skin (a condition called “leukemia cutis”). As a result, infant patients typically need to be treated with intensive chemotherapy regimens. However, infants are very vulnerable to treatment-related toxicities, and newer, less-toxic treatments continue to be studied in clinical trials.

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

- Pediatric regimens are more intense and complex than those given to adults.
- Pediatric regimens tend to use more **pegaspargase**, **vincristine** and corticosteroids. In contrast, adult regimens tend to use more **cyclophosphamide** and anthracyclines, such as **doxorubicin** and **daunorubicin**.
- Pediatric treatments are given for longer periods of time than adult regimens. Central nervous system treatment (CNS prophylaxis) is started earlier and given longer. Some children receive maintenance therapy for up to 3 years, while adults usually receive 2 years of maintenance therapy.

In clinical trials, researchers have started looking into the use of a variety of pediatric protocol options for older adolescent and young adult patients. They have found that AYA patients treated with pediatric protocols have better rates of survival compared to the same-aged patients treated with adult ALL protocols.

Down Syndrome. Down syndrome occurs in people who have an extra copy of chromosome 21, also called “trisomy 21.” Children with Down syndrome have an increased risk of developing ALL during childhood compared to children without Down syndrome.

Historically, children with ALL and Down syndrome have been shown to have poorer outcomes compared with children who have ALL but who do not have Down syndrome. Children with Down syndrome have an increased sensitivity to chemotherapy and are more likely to suffer complications from chemotherapy (including death) due to the side effects of treatment. Additionally, some studies have suggested that children with Down syndrome may have a higher chance of ALL relapse.

Children with Down syndrome who have ALL require special attention. They particularly need treatment protocols that are not only effective but less toxic than traditional treatments used for childhood ALL. These children can benefit from being treated at a major children’s hospital where the doctors have experience treating other Down syndrome children and are aware of the special care that they require.

Refractory and Relapsed ALL. Some patients have residual leukemia cells in their bone marrow even after they receive intensive treatment. In these cases, the disease is referred to as “refractory” (or “refractory ALL”). Other patients achieve remission but later have a return of leukemia cells in their bone marrow. This is referred to as a “relapse” of the disease (or “relapsed ALL”). Treatment for relapsed and refractory ALL is typically more intensive than for newly diagnosed patients.

Ph-Negative ALL. For patients with relapsed or refractory Ph-negative ALL, the following are some possible treatment options suggested by the NCCN guidelines:

- **Blinatumomab (Blincyto®)**
- **Tisagenlecleucel (Kymriah®)**
- **Inotuzumab ozogamicin (Besponsa®)**
- Combination regimens that include several chemotherapy drugs, some of which may have been given in the past

- Chemotherapy regimens using different drug combinations, may also be tried. The following drugs may be part of these regimens:
 - **Nelarabine** for patients with T-cell ALL
 - **Clofarabine**-containing regimens (e.g., **clofarabine, cyclophosphamide, etoposide**)
 - **Fludarabine**-based regimens (e.g., **fludarabine, cytarabine, G-CSF, idarubicin**)
 - High-dose **cytarabine**-based regimens (e.g., **high dose cytarabine, pegaspargase**)
 - Allogeneic stem cell transplantation is an option for healthy patients who have an available donor

Ph-positive ALL. For patients with relapsed or refractory Ph+ ALL, there are several treatment options. A patient may receive a different TKI than what they have taken before.

New mutations in the *BCR-ABL1* gene may occur over time. Some mutations can lead to resistance to certain TKIs. Before a patient starts treatment, *BCR-ABL1* mutation testing should be done to look for new mutations that may cause certain TKIs to stop working. Each TKI works in a slightly different way. One TKI may be able to counteract a mutation that another TKI cannot. Results of the gene mutation test may explain why a TKI used for a person's initial treatment stopped working. That patient may then receive a different TKI.

Other treatment options may include:

- **Blinatumomab**, for patients with ALL that has not responded to two or more TKIs
- **Tisagenlecleucel**, for B-cell ALL patients who are younger than 26 years and have refractory disease or have had two relapses
- **Inotuzumab ozogamicin**, which is being studied in clinical trials
- Allogeneic stem cell transplantation is an option for healthy patients who have an available donor

Talk to your doctor about

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

Research and Clinical Trials

New treatment approaches for ALL are under study in clinical trials. Researchers are studying novel strategies to improve the cure rate and minimize the side effects and late effects associated with current treatments, such as second cancer risk, damage to the heart and lungs and infertility. There are clinical trials for newly diagnosed patients, for patients with advanced disease, and for patients who are either resistant to or unable to tolerate their current medications. Many of the trials are being supported by LLS research programs.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time you discuss treatment options with your child’s doctor. The outcomes of patient participation in past clinical trials have resulted in the therapies we have today.

LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is a possible treatment option. When appropriate, patients and their caregivers can work with LLS Clinical Trial Nurse Navigators who will help find appropriate clinical trials and personally assist throughout the entire clinical trials process. Please visit www.LLS.org/CTSC for more information.

Research Approaches. A number of approaches are under study in clinical trials for the treatment of patients with ALL.

Genetics of Leukemia. Researchers are studying how changes (mutations) to the DNA inside normal bone marrow cells can cause them to develop into leukemia cells. There is a need to identify these genetic variations and customize treatment options based on the genetic characteristics of the leukemia cells. Newer techniques in gene sequencing have revealed previously unknown mutations that may be involved in the development of ALL. This information will help researchers develop new targeted therapies that are tailored to specific disease characteristics in each child.

New Drugs and Treatment Regimens. Researchers are working to develop effective and safer treatments for ALL. New treatments are needed for children with high-risk ALL and children with relapsed and refractory disease. ALL treatment can be very effective for most children, but it does not cure all children who have this disease. Researchers are studying new drugs for ALL, as well as the use of existing drugs given in different doses and with different methods of administration. Treatment approaches under investigation include:

- Chemotherapy. Chemotherapy is still the main treatment for most cases of ALL. Researchers are now studying different combinations of chemotherapy drugs to determine which is most effective while also limiting side effects, and are continuing to modify and reformulate traditional chemotherapy drugs to improve overall survival. They are also evaluating combinations of chemotherapy drugs with newer targeted therapies.
- Stem cell transplantation. Researchers continue to study stem cell transplantation to try to increase cure rates for ALL patients, reduce complications and determine which patients are most likely to benefit from this treatment.
- Targeted therapy. This is a type of treatment that uses drugs or other substances to block the action of certain enzymes, proteins or other molecules involved in the growth and survival of cancer cells, while causing less harm to healthy cells. Targeted agents under study include:
 - Proteasome inhibitors, such as **bortezomib (Velcade®)** and **carfilzomib (Kyprolis®)**
 - Tyrosine kinase inhibitors (TKIs), such as **ruxolitinib (Jakafi®)**
- Immunotherapy. Immunotherapy treatments use substances that can stimulate and/or suppress the immune system to help the body fight cancer. Agents under study include:
 - Bispecific T-cell engager (BiTE) antibodies, such as **blinatumomab (Blincyto®)**
 - Antibody drug conjugates, such as **inotuzumab ozogamicin (Besponsa®)**
 - Chimeric antigen receptor (CAR) T-cell therapy, such as **tisagenlecleucel (Kymriah®)**

Patients and their families who want to learn more about clinical trials visit www.LLS.org/CTSC or call an LLS Information Specialist at (800) 955-4572.

Related Disease

Mixed Phenotype Acute Leukemia (MPAL). MPAL is a subtype of acute leukemia of ambiguous lineage. It is an uncommon type of leukemia that can express surface proteins of two leukemias at the same time, most often B-cell ALL or T-cell ALL and acute myeloid leukemia (AML). It accounts for 2 to 5 percent of all acute leukemias, affecting patients of all ages, and includes several different subtypes.

The best therapy for patients with MPAL was previously not well known. More recent studies suggest that ALL chemotherapy regimens are more effective than AML regimens for most patients with MPAL. Some clinical trials are now including MPAL patients to receive ALL-type therapy. Developing the best treatment approach involves considering a variety of factors including the patient's age, medical history, presence of other relevant medical conditions, and the characteristics of the leukemic cells, as determined by immunophenotyping and genetic testing.

Patients and their families who want to learn more about clinical trials can visit LLS.org/CTSC or call an LLS Information Specialist at (800) 955-4572.

Side Effects and Complications

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

For children with severe or prolonged low red blood cell and platelet counts, transfusions of red blood cells and platelets may be needed. Blood cell counts usually return to normal levels after the transfusion(s). Red blood cell and platelet transfusions are almost always needed for several weeks during treatment. After that, the blood cell counts usually return to normal levels.

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

Because of the increased risk of infection during treatment, medical staff, family and friends 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 children who have central lines or ports need to be meticulous when cleaning insertion sites and catheters as instructed by their medical team.

Seek medical attention immediately if any signs of infection develop at home. A temperature of 100.4°F or higher or the onset of chills may be the only sign of infection. Other signs of infection may include persistent coughing, sore throat, pain during urination, or diarrhea.

Patients who have ALL are advised to receive certain vaccinations. It is recommended that children receive an annual influenza (flu) vaccine.

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

Uric acid is one of the chemicals released by 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. Children 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 children with ALL at the time of diagnosis or during a relapse, due to the infiltration of leukemia cells in the bone marrow. Rarely, some chemotherapy medicines used for patients with ALL can cause peripheral neuropathy, a nerve problem that can cause pain, numbness and tingling usually in the hands or feet. Use of pain medications and physical therapy are very effective approaches for patients with pain from leukemia or leukemia treatment.

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

- Hair loss
- Rashes
- Itchy skin
- Mouth sores
- Diarrhea

- Nausea and vomiting
- 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 to prevent or relieve this distressing side effect.

The use of corticosteroids, such as **prednisone** and **dexamethasone**, is a main component of virtually every induction therapy regimen for ALL. These drugs are also frequently incorporated into consolidation and maintenance therapy regimens. Acute 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. Gastric ulcers are another potential 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 reduce the risk of gastric ulceration.

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

Sometimes drugs or drug combinations cause side effects that continue after treatment ends. Some effects may be long-lasting (see *Long-Term and Late Effects of Treatment* on page 50).

Coping with Hair Loss in Children

For many children, hair loss can be one of the most distressing side effects of cancer treatment. Children can be sensitive about how they look and how others perceive them. Unfortunately, most children treated for ALL will begin to temporarily lose their hair 2 to 3 weeks after starting chemotherapy. The following information may be useful to help children cope with hair loss.

- Many children's hospitals work with organizations that help provide wigs and other head coverings to patients in need. A hospital social worker can help children explore their options, and help families understand what is or is not covered by insurance.
- If your child is planning on wearing a wig, take a picture of your child's hair (how it is usually worn) before hair loss occurs so a wig stylist can create a wig similar to your child's natural hair. In addition, you may want

to snip and keep a lock of your child's hair to help match the color and texture for a wig.

- Some children cut their hair short or shave their head before their hair falls out. This may allow children to feel some control over their hair loss and make it somewhat less upsetting. Other children may want to wait and see what happens. They may also want to dye their hair a wild color or get a crazy hairstyle. However, it is important to check with your child's doctor before using any dyes or chemical products on the hair.
- Some children like to wear wigs, hats, caps, scarves or turbans. Consider different head coverings. Shopping for head coverings can give your child some sense of control.
- Some children, particularly younger ones, may decide not to cover their heads. It is a personal choice for children and their families. However, for children going outside in the sun, it is important to protect the very sensitive skin on their head with either a head covering or sunscreen.
- Hair loss can be very difficult for children going back to school. Hospital social workers can offer support and resources for children dealing with hair loss.

Follow-Up Care

All children treated for ALL need to receive follow-up care. Follow-up care involves regular medical checkups after your child has finished treatment. These checkups may include blood work as well as other tests to check for a possible relapse of the cancer. These visits are also a time for doctors to test for other physical or emotional problems that may develop months or years after treatment. Even if your child is feeling entirely well, it is very important to keep the follow-up appointments.

After your child completes treatment for ALL and is in remission, follow-up tests are given to check how well the treatment worked and to look for signs of relapse. The tests can also determine how well the child's organs are working. This is important because ALL and its treatment can damage organs.

Your child will undergo frequent testing during the first year after treatment, but follow-up tests are done less often during the second and third years. As time goes on, less frequent testing and checkups may be required, but scheduled follow-up visits should continue indefinitely. If your child participates in a clinical trial, the follow-up care may be slightly different and should be followed accordingly.

Each patient has a different follow-up care schedule. How often your child has follow-up visits is based on your child’s type of cancer, overall health and the treatments he or she received. For children with ALL, the National Comprehensive Cancer Network (NCCN) recommends the following tests during the first 3 years after treatment ends, See **Table 5** below.

Table 5. 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
	• Bone marrow aspirate and cerebrospinal fluid testing if there is a suspected relapse	As needed
	• For patients with Ph+ ALL, testing of the <i>BCR-ABL1</i> gene for mutations	Periodically
Year 2	• Physical exam including testicular exam for males	Every 3 to 6 months
	• CBC with differential	Every 3 to 6 months
	• Bone marrow aspirate and cerebrospinal fluid testing if there is a suspected relapse	As needed
	• For patients with Ph+ ALL, testing of the <i>BCR-ABL1</i> gene for mutations	Periodically
Year 3 and on	• Physical exam, including testicular exam for males	Every 6 to 12 months
	• CBC with differential	Every 6 to 12 months
	• Bone marrow aspirate and cerebrospinal fluid testing if there is a suspected relapse	As needed
	• For patients with Ph+ ALL, testing of the <i>BCR-ABL1</i> gene for mutations	Periodically

Adapted from National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology: Pediatric Acute Lymphoblastic Leukemia 2020.

It is important to keep a record of your child’s cancer treatments, so the doctor can follow up on specific late effects that may be associated with those treatments.

Your child’s healthcare team may also recommend a schedule for having your child’s learning skills tested. If your child appears to be struggling with learning, special education methods may help. See *Returning to School* on page 52.

Your child's need for follow-up care will continue even after becoming an adult. Young adult patients need to be educated about the importance of follow-up care. Remind your young adult that any new providers will need to know his or her detailed medical history and survivorship care plan. Work with members of the cancer treatment team to coordinate care and transfer medical records to new providers.

Survivorship Care Plan. Generally, “survivorship” refers to the health and well-being of a person after cancer treatment. Your child's oncologist will help create a survivorship care plan for your child to guide follow-up care. Share the survivorship care plan with any healthcare providers your child sees. The survivorship care plan should include the following information:

- A list of all your child's healthcare providers: pediatrician, hematologist-oncologist, radiation oncologist, others
- Diagnosis summaries with specifics such as stage, sites of involvement, and molecular or genetic markers
- Treatment summaries with specifics such as dates of treatment, names of chemotherapy or other drugs received, radiation dosage and site, responses to treatments and side effects
- Follow-up appointment schedule with the names of the medical providers and how often the appointments should occur
- Schedule for ongoing monitoring, with recommended tests and frequency
- List of possible long-term and late effects
- Health and wellness lifestyle recommendations, such as nutrition, exercise, other cancer and disease screenings, and referrals to specialists (as needed) to assist with these recommendations

The Children's Oncology Group provides a downloadable Summary of Cancer Treatment template to fill out with your child's healthcare team. Visit www.survivorshipguidelines.org to download a template.

The Passport for Care Survivor Website offers free access to resources, education and tools for survivorship for childhood cancer survivors. Visit www.cancersurvivor.passportforcare.org to learn more.

Survivorship Clinics. Childhood cancer survivors have special lifelong healthcare needs. Many hospitals and treatment centers offer survivorship clinics that specialize in long-term follow-up care for cancer survivors. Childhood cancer survivors often begin visiting a survivorship clinic 2 years after finishing treatment. However, the timeline can differ based on your child's unique needs and medical history. Additionally, coordination between members of your child's cancer survivorship healthcare team and primary care pediatrician is essential.

Your child should visit the survivorship clinic and his or her primary care pediatrician at least once a year for a complete physical examination and any additional tests, even when feeling well. Regular visits allow the doctor to:

- Assess the full effects of therapy
- Identify and manage long-term and late effects of treatment (see *Long-Term and Late Effects of Treatment* below)
- Detect and treat disease recurrence

In preparation for your child's visits, keep a record of the physical or emotional symptoms that your child experiences so that you can discuss them with members of the healthcare team.

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

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 problems that do not appear until years, or even possibly decades, after treatment ends.

Cancer treatments may harm your child's organs, tissues or bones and can cause health problems later in life. Children and young adults who have been treated for ALL may be at increased risk for developing a second cancer, heart damage and neurologic and/or cognitive problems. Patients should see a primary care doctor for a general health examination at least once a year. They should also be examined regularly by an oncologist.

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

Second Cancer Risk. Survivors of childhood ALL are at an increased risk for developing a second cancer later in life. A second cancer may occur months or years after treatment is completed. Because of this risk, it is important for patients who have been treated for ALL to get routine cancer screenings.

These cancer screenings should be a shared responsibility between your child's primary care doctor and oncologist. In addition, lifestyle modifications that reduce the risk for a second cancer should be encouraged, such as exercising, maintaining a healthy weight and not smoking.

Cardiovascular System. Most ALL patients are treated with an anthracycline, such as **doxorubicin** or **daunorubicin**. 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. Talk to your child's doctor about whether tests are needed to check for signs of heart and blood vessel-related late effects. If tests are recommended, find out how often they should be done.

Osteonecrosis. Osteonecrosis, also called "avascular necrosis," is a condition in which there is a reduced blood flow to the bones. This can cause parts of the bones to weaken or die, which can cause pain or even breaks in the bone. Osteonecrosis often affects weight-bearing joints, such as the hip bones and/or knees. Osteonecrosis is a long-term side effect associated with corticosteroid therapy. This condition seems to have a higher incidence among adolescents than in younger children or adults (likely due to skeletal growth). Your medical team may recommend checking vitamin D and calcium levels if your child is at risk for this condition. If your child is having pain, imaging studies may be indicated or may be performed as part of a clinical trial.

Central Nervous System. Treatments directed at the central nervous system, such as intrathecal chemotherapy, intravenous chemotherapy with high-dose **methotrexate** or **cytarabine** that can cross the blood-brain barrier and radiation to the brain, are effective therapies used to treat children with ALL. However, these treatments can increase the risk for cognitive effects, such as long-term memory and concentration problems. Cognitive late effects can affect your child's ability to learn and think.

Children may experience side effects of treatment, both in the short and long term, which can affect learning, growth, cognitive development and psychosocial development. When children return to school, there will be new challenges facing families whose focus up to that point had been getting their child through treatment. By being aware of possible side effects, parents can work with school personnel to help their children cope and manage schoolwork.

Visit www.LLS.org/FamilyWorkbook to find additional information about long-term and late effects (in the chapter *Beyond Treatment*).

Talk to your doctor about

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

Returning to School. School is a place for learning and fun, so children benefit from returning to their classrooms as soon as medically possible. Most children who have cancer will attend school at least some of the time during their treatment. Yet returning to school after a diagnosis of cancer can be a tough adjustment. Your child may have reservations about returning to school, including fears about:

- The reaction of friends and other children at school
- Missed schoolwork and social activities
- Changes in his or her abilities
- Changes in his or her appearance

Discuss any fears your child may have before he or she goes back to school. Help him or her develop coping strategies for situations that he or she might face.

If your child has been out of the classroom for an extended time, it may be helpful to ease him or her back into full-time school slowly. For example, your child may attend school for half days or every other day during the first weeks back. Talk to school administrators about adjustments to schedules and other options available for your child.

Take the following steps to ensure that your child gets the support he or she needs at school:

- Meet with school administrators, teachers, counselors and the school nurse as soon as you can after diagnosis to discuss your child's medical condition and address any special needs or concerns with them.
- Discuss any evaluations that may need to be done to provide your child with extra support, such as neuropsychological testing. Ask school staff members to promptly provide you with relevant information when they identify any issues that arise.
- Work with the school nurse to make sure that a care plan is in place that addresses your child's medical needs during school hours.
 - For example, your child may need to take medications at school. These may be daily medications or medications taken as needed (for example, if your child feels nauseated).
 - If your child has a catheter or some other medical device in place, make sure the school nurse knows how to care for the device properly.
 - The care plan should also include a list of issues that can come up, reasons to contact you and when to call for emergency care. Your child's healthcare team can help the school nurse develop a care plan and fill out any necessary paperwork.

- Ask your child's doctor to write a letter outlining your child's physical limitations or medical needs, such as the need for an extra snack or cool drink, extra bathroom breaks and/or a safe place to rest, as needed. Your child may also need modifications for recess or physical education (P.E.) classes. Meet with school administrators and teachers to discuss these needs and how they will be accommodated. Ask your child's healthcare team for their expertise in explaining this information.
- To reduce your child's anxiety, arrange meetings with his or her teacher(s) before he or she goes back to school.
- Ask about providing an age-appropriate class presentation, either before or after your child returns to school, to educate friends and classmates about the illness. Ask the healthcare team for assistance. Some treatment centers have healthcare professionals available to lead these presentations, or have versions of these presentations available. Ask your child if he or she would like to be present for the presentation. If so, your child can participate in ways that are comfortable for him or her.

For more information about returning to school after cancer treatment, visit www.LLS.org/booklets to view *Learning and Living with Cancer*.

The Trish Greene Back to School Program. This LLS program offers free information and materials to parents and educators that can help ease a child back into school. The program was developed to encourage communication among parents, patients, healthcare professionals and school personnel to assure that children have a smooth transition from undergoing active treatment to settling back into school. Call an LLS Information Specialist at **(800) 955-4572** to learn more.

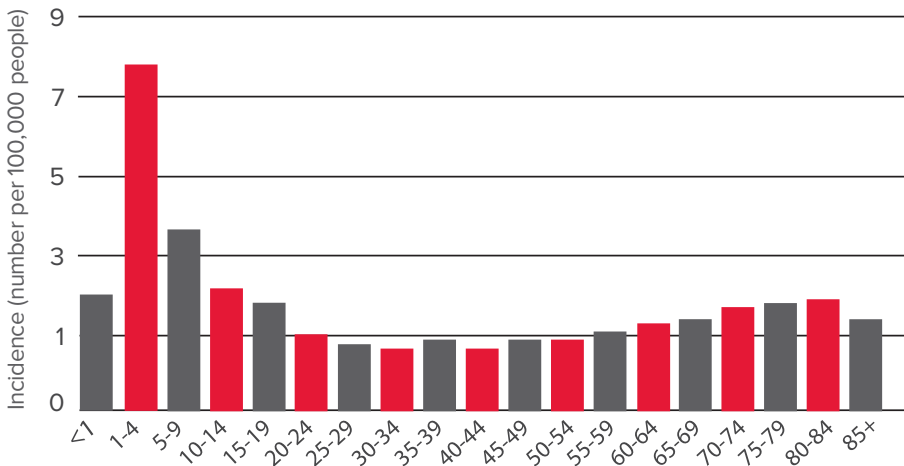
Treatment Outcomes. A few decades ago, there were very low cure rates in both children and adults diagnosed with ALL. Today, childhood ALL has one of the highest cure rates of all childhood cancers, approaching 92 percent for children younger than 15 years and more than 94 percent for children younger than 5 years.

Incidence, Causes and Risk Factors

Incidence. ALL is rare in children. An average of 2,761 children and young adults younger than 20 years of age were diagnosed with leukemia each year from 2012 to 2016 in the United States.

There is an unusual age distribution among people with ALL. The incidence of ALL peaks between the ages of 1 and 4 years and then decreases until about age 55 years. The median age at diagnosis is 15 years. About 52 percent of the patients diagnosed are younger than 20 years at the time of diagnosis. See **Figure 5** below.

Figure 5. Acute Lymphoblastic Leukemia (ALL): Age-Specific Incidence Rates 2012-2016



The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of acute lymphoblastic leukemia each year per 100,000 people, by age-group. Note that the risk of ALL is greatest in the first 5 years of life. An increase in occurrence is also seen in older individuals.

Source: Surveillance, Epidemiology and End Results (SEER) Program; National Cancer Institute; 2019.

Causes and Risk Factors. In most cases, it is not clear what causes the genetic changes that lead to ALL, particularly in children. 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 usually occur during a person’s lifetime, rather than being inherited from a parent.

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. However, having a risk factor 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 may develop the disease. ALL is not contagious.

Factors associated with an increased risk of developing ALL include:

- Genetic disorders. Some genetic disorders, particularly Down syndrome (trisomy 21), are associated with an increased risk of ALL. Although rare, other genetic conditions have been categorized as risk factors for developing leukemia (ALL or AML). These include neurofibromatosis, Klinefelter syndrome, Fanconi anemia, Shwachman-Diamond syndrome, Bloom syndrome and ataxia-telangiectasia.
- Age. The highest incidence rates for ALL are seen in children and adolescents younger than 15 years. Within this group, the highest rate is in children aged 1 to 4 years.
- Gender. Boys are more likely to develop ALL than girls.
- Race/ethnicity. In the United States, ALL is more common in Hispanics and whites.
- 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. However, this is not common in children.

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:

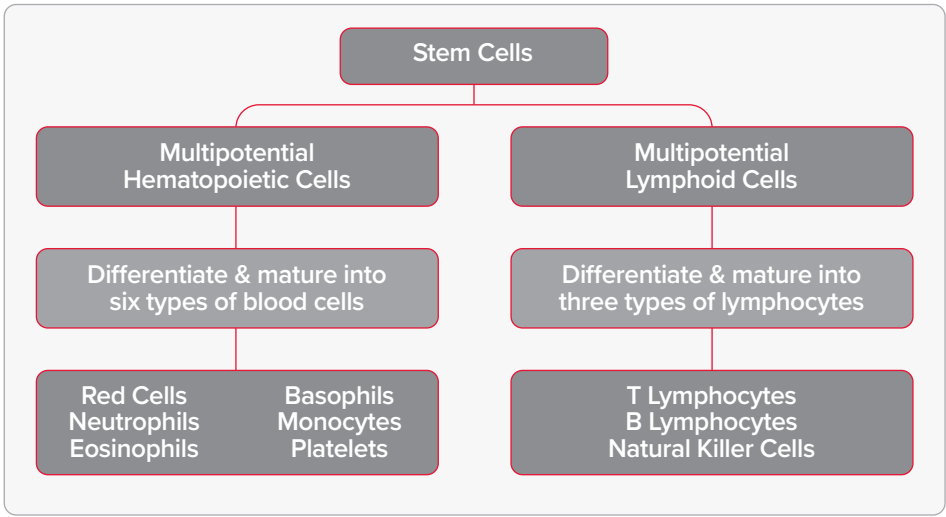
- Proteins
 - Albumin, the most common blood protein
 - Blood-clotting proteins (coagulation factors) made by the liver
 - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
 - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid hormone 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.” The blood cells are suspended in the plasma. See **Figure 6** on page 57.

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

1. Red blood cells (the cells that carry oxygen)
 - These make up a little less than half of the body’s total blood volume.
 - They 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 (cells that help blood clot)
 - These are small cells (one-tenth the size of red blood cells).
 - They help stop bleeding from an injury or cut.
 - They 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 (or WBCs, the cells that fight infections), including:
 - Neutrophils and monocytes. These are cells called “phagocytes” 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 are the WBCs that respond to allergens or parasites.
 - Lymphocytes. These are the WBCs found mostly in the lymph nodes, spleen and lymphatic channels that 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 cells (NK cells)

Figure 6. Blood Cell & Lymphocyte Development



Stem cells develop into blood cells (hematopoiesis) and lymphocytic 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 marrow and then circulate 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, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull. Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

Resources and Information

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

For Help and Information

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

- Call: (800) 955-4572 (Monday through Friday, 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
- Visit: www.LLS.org/InformationSpecialists

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

Free Information Booklets. LLS offers free education and support booklets that can be either 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 assistance to individuals with blood cancer. Please visit www.LLS.org/finances for more information.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

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

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Please visit www.LLS.org/HealthManager to download for free.

LLS Coloring for Kids™. This free coloring app allows children to express their creativity and offers activities to help them learn about blood cancer and its treatment. The app includes blank canvases, general coloring pages and pages from LLS coloring books. This app can be used anywhere and may help pass

time in waiting rooms or during treatment. Visit www.LLS.org/ColoringApp to learn more and download.

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

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

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

Continuing Education. LLS offers free continuing education programs for health care professionals. Please visit www.LLS.org/ProfessionalEd for more information.

Community Resources and Networking

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. Please visit www.LLS.org/community to join.

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

LLS Chapters. 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 chapter, please

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

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 obtain our directory.

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

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

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 a language interpreter or 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 (select option 4)
- Visit: www.publichealth.va.gov/exposures/AgentOrange

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

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

For more information, please

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

People Suffering from Depression. Treating depression has benefits for cancer patients. 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. Enter “depression” in the search box.

Health Terms

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

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

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

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

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

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

Autologous Stem Cell Transplantation. A treatment in which stem cells are removed from a patient, stored and then returned to the patient's body after intensive treatment cancer treatment. This type of transplantation is virtually never used for children with ALL. **See the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

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

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

Blast Cell. An immature blood cell.

Blood Cell Count. See Complete Blood Count.

Blood Cells. There are three main 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. A spongy tissue in the hollow central cavity of the bones, where blood cells form.

Bone Marrow Aspiration. A procedure in which a sample of liquid bone marrow is removed for examination by a pathologist. After the patient is given a numbing agent, the sample is taken (usually from the patient's hip bone) using a special needle. Bone marrow aspiration and bone marrow biopsy are often done at the same time, and may be done in the doctor's office or in a hospital. When this procedure is done in children, they are usually under sedation or general anesthesia.

Bone Marrow Biopsy. A procedure in which a sample of bone with bone marrow is removed for examination by a pathologist. The sample is usually taken from the hip bone. After medication is given to numb the skin and tissue, a special hollow biopsy needle is used to remove a core of bone containing marrow. Bone marrow aspiration and bone marrow biopsy are often done at the same time, and may be done in the doctor's office or in a hospital. When this procedure is done in children, they are usually under sedation or general anesthesia.

CBC. See Complete Blood Count.

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

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

Chemotherapy. Treatment that stops the growth of cancer cells, either 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 eventually re-infused into the patient's blood stream. **See the free LLS fact sheet *Chimeric Antigen Receptor (CAR) T-Cell Therapy*.**

Chromosome. Part of the cell that contains genes in a linear order. Human cells have 23 pairs of 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. A treatment that is proven to be safe and effective in a clinical trial is often approved by the United States Food and Drug Administration (FDA) for use as a standard treatment, if it is either more effective or has fewer side effects than the current standard treatment.

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

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

Conditioning Therapy. Intensive treatment used to prepare a patient for stem cell transplantation. The treatment consists of high-dose chemotherapy and/or total body radiation.

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 a treatment response in patients.

Differentiation. The process in which immature cells develop and mature into cells with specific functions. Blood stem cells mature into red blood cells, platelets or white blood cells. See Hematopoiesis.

DNA. Abbreviation for deoxyribonucleic acid, the molecules found inside cells that carry genetic information. DNA is passed to new cells during the process of cell division. A change or mutation in the DNA can lead to cell death, changes in the 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 travels to affected areas during infections and allergic reactions.

Erythrocyte. See Red Blood Cell.

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

FISH. See Fluorescence in Situ Hybridization (FISH).

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

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.

Frontline Therapy. The first treatment given for a disease.

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

Hematologist. A doctor who specializes in treating blood cell diseases.

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

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

Hematopoietic Stem Cell. An immature cell that can develop into any type of blood cell: a red blood cell, a white blood cell or a platelet. Also called a “blood stem cell.”

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 to distinguish its own cells from foreign cells. HLA factors are inherited from a person’s mother and father. HLAs make up an individual’s tissue type, which varies from person to person. They are a critically important factor in allogeneic (donor) stem cell transplantation. Before transplantation takes place, HLA typing is performed in order to determine if the donor’s cells are compatible with the recipient’s cells.

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

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

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

Immunophenotyping. A process that uses antibodies to find specific types of cells based on the types of antigens (markers) on the surface of the cells.

Immunotherapy. The term for several treatment approaches used by doctors to harness the body’s immune system to treat leukemia and other diseases. These therapies include antibody therapies (monoclonal, bispecific and antibody-drug conjugates), radioimmunotherapy and cellular therapy.

Intrathecal. The designation for the fluid-filled space between the thin layers of tissue that cover the brain and the spinal cord, called the “meninges.” In some situations (for example, when leukemia cells are in the meninges), drugs are administered directly into the spinal canal. This treatment is called “intrathecal therapy.”

Karyotype. An organized profile of a person’s chromosomes. It exhibits the size, shape and number of chromosomes in a cell.

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

Leukocyte. See White Blood Cell.

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

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

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 (B cells) in making antibodies; and 3) natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Lymphoid. Referring to lymphocytes (a type of white blood cells).

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

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

Marrow. See Bone Marrow.

Minimal 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 cells can only be identified by very sensitive tests. **See the free LLS fact sheet *Minimal Residual Disease*.**

Monoclonal Antibody. A type of synthetic protein that can bind to substances in the body, including cancer cells. Monoclonal antibodies are used in cancer treatment to target cancer cells.

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

Monocyte/Macrophage. A type of white blood cell that is made 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 their 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 neutropenia 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 blood cancer, or who have received treatment (such as chemotherapy) for cancer, often have low neutrophil counts.

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

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

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

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

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

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

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

Polymerase Chain Reaction (PCR). A very sensitive genetic laboratory technique used to detect and measure some genetic mutations and chromosomal changes that are too small to be seen with a microscope. PCR testing essentially increases (amplifies) small amounts of specific pieces of DNA so that they are easier to detect and measure. This test can detect the presence of one blood cancer cell among 500,000 to 1,000,000 healthy blood cells.

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

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

Protocol. A plan for medical treatment.

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

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

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

Refractory Cancer. Cancer that does not go into remission or improve substantially after 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 instructions in DNA (deoxyribonucleic acid) for making proteins.

Spinal Tap. See Lumbar Puncture.

Spleen. An organ in the left upper portion of the abdomen, just under the left side of the diaphragm. The spleen filters blood, stores blood cells and destroys old blood cells. Enlargement of the spleen is called “splenomegaly.”

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

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation and Autologous Stem Cell Transplantation.

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

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

Transfusion. A procedure in which whole blood or parts of blood are placed 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.

Treatment Cycle. A course of treatment followed by a period of rest (to allow the body to recover) that is repeated on a regular schedule. For example, chemotherapy given daily for 1 week followed by 2 weeks of rest, may be one patient’s cycle of treatment.

Trisomy. The presence of a third chromosome, instead of the normal two, in some or all of the body's cells. Down syndrome is a condition caused by trisomy. People with Down syndrome typically have three copies of chromosome 21 in each cell (normally there are two copies of chromosome 21).

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, including cell growth and division. These enzymes may be too active, or found at high levels, in some types of cancers. TKIs work to block these over-active enzymes and may stop cancer cells from growing.

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

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

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