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Chronic Lymphocytic Leukemia: In Detail

A companion to the booklet CLL: The Basics

Revised **2025**

Formerly titled Chronic Lymphocytic Leukemia

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Acknowledgement

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common chronic leukemia in adults. Doctors have learned a great deal about CLL in the last few decades. Advances in the treatment of CLL have resulted in improved remission rates, quality of life and survival for patients. However, more work needs to be done. Researchers continue to study and develop new therapies in clinical trials to treat CLL.

This booklet provides information about CLL for patients and their families. It also includes brief descriptions of blood, bone marrow and the lymphatic system, as well as definitions of health terms related to CLL.

For easy-to-read, general information about chronic lymphocytic leukemia for yourself, family or friends, visit www.LLS.org/booklets to view *CLL: The Basics*.

While this booklet focuses on CLL, there is a type of non-Hodgkin lymphoma (NHL), called "small lymphocytic lymphoma (SLL)," which most experts consider to be the same disease as CLL. While SLL starts in the same kind of cells that cause CLL, it is localized in lymph nodes at diagnosis. Patients with SLL generally benefit from treatment with CLL-like regimens, rather than traditional lymphoma therapy. So, if you have been diagnosed with SLL, this booklet will also have helpful information for you.

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

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Leukemia Basics

Leukemia is a type of cancer. “Cancer” is a term for diseases in which abnormal cells grow uncontrollably and can spread to other parts of the body. Cancer can start anywhere in the body. Leukemia is a cancer of the blood and bone marrow.

There are three main types of blood cells: red blood cells, white blood cells and platelets. Red blood cells carry oxygen throughout the body. White blood cells help fight infections. Platelets help stop bleeding by clotting (clumping together) at the site of an injury.

Blood cells are made in the bone marrow, the spongy tissue in the center of most bones. The bone marrow contains immature cells (stem cells) that eventually develop into blood cells. Leukemia forms when one of the blood cells in the bone marrow mutates (changes). This causes the blood cell to grow uncontrollably. This results in a 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, making more leukemia cells. Over time, the leukemia cells crowd out and suppress the development of normal healthy blood cells in the bone marrow. As a result, the body does not have enough healthy red blood cells, white blood cells and platelets. When this happens, the body’s organs and tissues may not receive enough oxygen to work properly. Also, the body may not be able to fight infections or form blood clots when needed.

The four major types of leukemia are:

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

Doctors classify leukemia based on:

- **The type of blood cell.** Leukemia is classified by the type of blood cell that becomes cancerous. The two primary types are lymphoid and myeloid. Lymphoid stem cells develop into a type of white blood cell called a “lymphocyte.” Myeloid stem cells can develop into red blood cells, platelets as well as other types of white blood cells (i.e., basophils, eosinophils, monocytes and neutrophils). Leukemia is classified as “lymphocytic” (or “lymphoblastic”) if the cancerous change starts in a lymphoid cell, or “myeloid” (or “myelogenous”) if the cancerous change originates in a myeloid cell. See **Figure 5** on page 45.

- **Rate of disease progression (meaning either how quickly or how slowly the leukemia grows).** Leukemias can be “acute” or “chronic.” Acute leukemias develop and grow rapidly, usually becoming worse quickly if they are untreated. Acute leukemias affect cells that are not fully developed. These immature cells cannot carry out their normal functions. Chronic leukemias usually progress more slowly than acute types of leukemia, and patients have greater numbers of mature cells. In general, these more mature cells can carry out some of their normal functions.

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

How Chronic Lymphocytic Leukemia (CLL) Develops. Lymphocytes are white blood cells that are part of the body’s immune system. There are three main types of lymphocytes: B cells, T cells and natural killer (NK) cells. Chronic lymphocytic leukemia is a cancer that starts in B cells, (also called “B lymphocytes”). Healthy B cells produce special proteins called "antibodies," which bind to foreign substances such as bacteria and viruses and mark them for destruction by other white blood cells.

Chronic lymphocytic leukemia results from one or more mutations in the DNA (deoxyribonucleic acid, the genetic material that is the building block of all cells) of a single bone marrow cell that would otherwise develop into a healthy B cell. Genetic errors in the mutated cell cause the leukemia cell (also referred to as a “CLL cell”) to keep growing and dividing, whereas a healthy cell would stop dividing and eventually die. Every cell that arises from the initial leukemia cell also has the mutated DNA.

These leukemia cells do not function like normal B cells that make antibodies. As a result, people with CLL usually have weakened immune systems and are more vulnerable to infections because they lack enough healthy B cells and their antibodies.

In addition to being ineffective, the leukemia cells accumulate in the bone marrow and slow down normal blood cell production. As a result, people with CLL may not have enough mature, healthy red blood cells, other white blood cells and platelets. Having low levels of blood cells may result in anemia, infections and excessive bleeding or bruising.

Over time, the leukemia cells can spill out of the bone marrow into the bloodstream. This can cause the number of white blood cells in the blood to increase, but most of these are leukemia cells that do not protect against infection. Once in the blood, the leukemia cells can spread to the lymph nodes and other organs in the body.

How Small Lymphocytic Lymphoma (SLL) Develops. Small lymphocytic lymphoma is a type of non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma is the term for several types of cancer that start in a lymphocyte in the lymphatic system (the network of organs and tissues, such as lymph nodes and spleen, that protects the body against disease and infection). The lymphatic system produces and releases lymphocytes that monitor and destroy bacteria, viruses and parasites that may enter the body.

In SLL, a genetic mutation causes abnormal B cells to build up and multiply, mostly in the lymph nodes. This causes the lymph nodes to swell and become larger than normal.

The abnormal lymphocytes in people with SLL are identical to those in people with CLL. According to the World Health Organization (WHO), CLL and SLL are considered the same cancer. They only differ by the location of the cancer cells. With CLL, the abnormal lymphocytes are found in the blood and bone marrow. They may also be in the lymph nodes and spleen. With SLL, there are few, if any, abnormal lymphocytes in the blood. Instead, they are found in the lymph nodes and spleen.

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate an illness or disease. A “sign” is a change that the doctor notices during an examination or notes in a laboratory test result. A “symptom” is a change that a patient can see and/or feel.

Approximately 70% of people with CLL are diagnosed with the disease before they have any symptoms. Chronic lymphocytic leukemia is often detected during a routine blood test. A high number of lymphocytes, a type of white blood cell, is often the first sign of CLL.

Generally, CLL symptoms develop over time. As the disease progresses, a person may experience symptoms such as:

- Infections
- Weakness or feeling tired
- Shortness of breath during normal physical activity
- Swelling of the lymph nodes in the neck, armpits, stomach or groin (top part of the inner thigh)
- Feeling of fullness below the ribs due to an enlarged spleen or liver
- Easy bruising or bleeding
- Petechiae (pinhead-sized red spots on the skin)

- B symptoms:
  - Fever when there is no infection
  - Drenching night sweats
  - Unexplained weight loss

Medical Tests

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

- Estimate how slowly or how quickly 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 results

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

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

Medical History. Your doctor will take a thorough medical history. The history may include information about past illnesses, injuries, treatments and medications. Some illnesses and cancers run in families, so the doctor may also ask about the health of your blood relatives. These include parents, grandparents, brothers and sisters. A family history of CLL or other blood cancers may increase your risk of developing CLL.

Physical Examination. The doctor will want to know about your current symptoms and will conduct a physical examination. During the examination, the doctor may listen to your lungs and heart and carefully examine your body for signs of infection and disease. To check the internal organs, the doctor may also feel different parts of your body. For example, the doctor may feel the abdomen to see if you have an enlarged spleen or liver. Because CLL can cause enlarged lymph nodes or spleen, the doctor may check the lymph nodes in your neck, armpits, stomach and groin.

Complete Blood Count 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 complete blood count (CBC) should include a differential (diff), which measures the numbers of the different types of white blood cells—basophils, eosinophils, lymphocytes (B cells and T cells), monocytes and neutrophils.

A high number of B cells, one type of lymphocyte, may indicate CLL. People with CLL have "lymphocytosis" (a higher-than-normal number of lymphocytes) with more than 5000 clones (monoclonal) of B lymphocytes/microliter in the blood. This is identified by a specialized test called flow cytometry, which sorts cells based on their chemical and physical characteristics. Most of these lymphocytes are leukemia cells that do not protect against infection. In addition, these patients may also have a low number of red blood cells and platelets.

Bone Marrow Aspiration and Biopsy. Leukemia starts in the bone marrow, the spongy tissue inside the center of most bones. Bone marrow aspiration and biopsy are procedures to collect and examine bone marrow.

Bone marrow has both a liquid and a solid component.

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

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

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

For a bone marrow aspiration, a special hollow needle is inserted through the back of the hip bone and into the bone marrow to aspirate (remove) a liquid sample of cells. For a bone marrow biopsy, a wider biopsy needle is used to remove a sample of a solid piece of bone marrow. Both needles are inserted through the skin, generally in the same area. Both bone marrow samples are sent to the laboratory where they are examined under the microscope.

To diagnose CLL, it is usually not necessary for doctors to do a bone marrow aspiration or biopsy. For most patients, this procedure is not recommended. Occasionally, bone marrow aspiration and biopsy may be recommended before treatment begins. The results of bone marrow tests can help rule out other diseases if the diagnosis is uncertain. These tests can also be used during treatment to evaluate its effectiveness.

Lymph Node Biopsy. Patients with enlarged lymph nodes may need to undergo a lymph node biopsy to determine whether their signs and/or symptoms are due to lymphoma, leukemia or some other condition. A lymph node biopsy is a procedure in which either all or part of a lymph node is removed and examined for signs of infection or disease such as cancer.

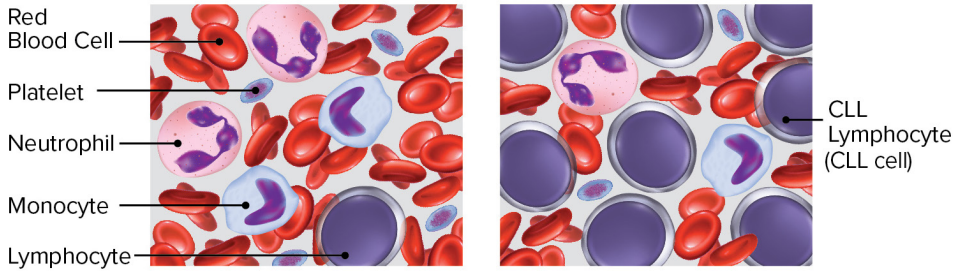
To ensure there is enough tissue to make an accurate diagnosis, the preferred methods for the lymph node biopsy are often "excisional" or "incisional." In an excisional biopsy, the whole lymph node is removed. In an incisional biopsy, only part of the lymph node is removed. If the lymph node is just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

In certain situations, a "core needle biopsy" may be necessary if the lymph node is too difficult to reach. In this method, a wide needle is used to remove a column of tissue from the lymph node. This is done after the area has been numbed with a local anesthetic. A "fine-needle aspiration biopsy" (another type of needle biopsy) may be inadequate for diagnosing CLL. The long thin needle used to draw fluid and cells in a "fine-needle aspiration" might not provide enough cells to make an accurate diagnosis.

Cell Assessment. At the laboratory, a pathologist examines the blood, bone marrow and/or lymph node samples. In addition, a "hematopathologist" may be consulted because they are doctors with special training in diagnosing diseases of the blood, bone marrow and lymphatic system.

The hematopathologist examines the cells under a microscope to determine their size, shape, type and to identify other cell features. Normal blood contains many different blood cells including white blood cells and platelets, but most of the cells are red blood cells. In patients with CLL, there are too many CLL cells and not enough red blood cells, other healthy white blood cells and platelets (see **Figure 1** below).

Figure 1. Healthy Blood Cells Versus CLL Cells



Left: Healthy blood contains red blood cells, white blood cells and platelets.
Right: In CLL, the CLL cells multiply uncontrollably resulting in too many leukemia cells and too few healthy blood cells.

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

Each person's cancer has a unique pattern of biomarkers. Biomarker testing may also be used to help plan treatment, find out how well treatment is working or predict whether cancer will come back or spread to other parts of the body.

Biomarker testing should be done when the cancer is first diagnosed and may also be done before beginning treatment and after a relapse. This is because it is possible for the CLL cells to acquire additional genetic abnormalities.

Biomarker tests for CLL include:

Immunophenotyping (Flow Cytometry). This lab test identifies cancer cells based on markers called "antigens." Antigens are proteins found either on the surface or within white blood cells. Finding (or not finding) certain antigens can help determine the type of leukemia. The pattern of the surface proteins is called the "immunophenotype."

In CLL, a blood sample is often used for this test, but it can also be done using cells from the bone marrow, lymph nodes and other tissues. In small lymphocytic lymphoma (SLL), a lymph node sample is often used.

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

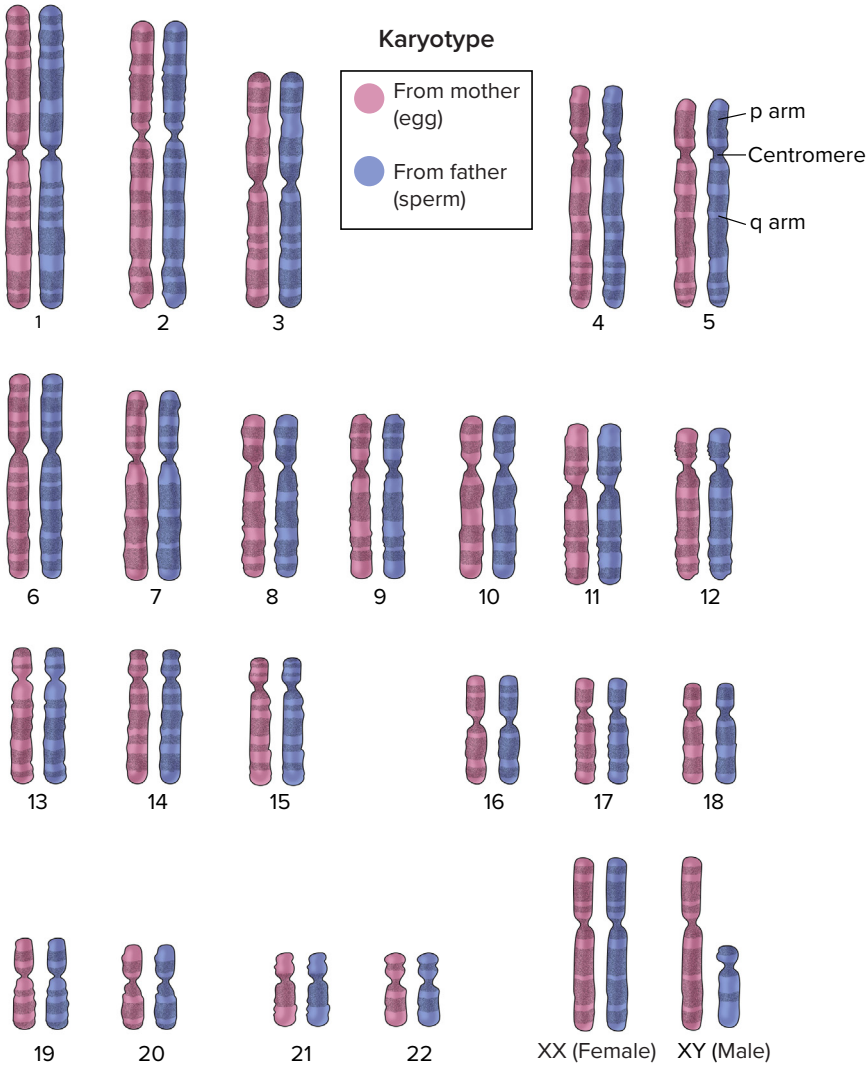
Leukemia cells have different antigens on their surfaces, depending on the type of leukemia. These antigens, called "cluster of differentiation (CD)," help further identify the type of leukemia cells. Flow cytometry is used to determine the type of lymphocytes (B cells or T cells) and to assess the maturity of the cells. In CLL, the immunophenotype includes CD5, CD19 and CD23 proteins.

Cytogenetic Analysis (Karyotyping). Cancer is a disease caused by mutations (changes) to the genetic material inside of cells. This genetic material is called DNA (deoxyribonucleic acid). Inside cells, DNA is packaged into thread-like structures called "chromosomes." In people with CLL, cytogenetic analysis is used to look for abnormal changes in the structure of the chromosomes within the leukemia cells.

Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure.

In many cases of CLL, the chromosomes of leukemia cells have abnormal changes that can be seen under a microscope. Cytogenetic testing can be done on leukemia cells from either a bone marrow sample or a blood sample. The leukemia cells in the sample are allowed to grow in the laboratory and then are stained. The stained sample is examined under a microscope and photographed to show the arrangement of the chromosomes, called a "karyotype." The karyotype shows if there are any abnormal changes in the size, shape, structure or number of chromosomes in the leukemia cells. See **Figure 2** below, for an illustration of a normal karyotype.

Figure 2. Normal Karyotype



Chromosomal abnormalities in CLL cells can be identified in many patients who have CLL. These abnormalities can be "numerical" or "structural." A numerical abnormality is when there is a different number of chromosomes in the cells than the number that is usually found. For example, instead of the typical 46 chromosomes in each cell of the body, there may be 45 or 47 chromosomes. A structural abnormality means the chromosome's structure has been altered. One common structural abnormality often found in CLL is a "deletion (del)." A deletion occurs when part of a chromosome is missing.

Fluorescence In Situ Hybridization (FISH). Doctors use this very sensitive test to detect certain abnormal changes in the chromosomes and genes of leukemia cells. Pieces of DNA that contain special fluorescent dyes are prepared in the laboratory and added to the leukemia cells on a glass slide. The pieces of DNA that bind to certain genes or areas of chromosomes light up when the slide is viewed under a specialized "fluorescence" microscope. Not only can FISH identify abnormal chromosome changes that can be seen with a microscope, but it can also detect some changes that are too small to be seen with basic cytogenetic testing. However, FISH is not used as a general screening tool, and this test has one disadvantage—the doctor must select the specific chromosomes or genes to examine before the test is performed. Cytogenetic abnormalities detected by FISH are present in more than 80% of patients with CLL. Some patients may have leukemia cells with an extra copy of chromosome 12, or they may have 11q, 13q or 17p deletions.

Polymerase Chain Reaction (PCR). This is another very sensitive lab technique. Doctors use it to detect and measure certain genetic mutations and chromosomal changes within the leukemia cells that are too small to be seen with a microscope. PCR essentially increases or "amplifies" small amounts of specific pieces of either RNA (ribonucleic acid) or DNA to make them easier to detect and measure. This test can find a single leukemia cell among more than 100,000 to 1 million healthy cells. PCR testing is another method used to determine a patient's measurable residual disease (MRD)—the small amount of cancer cells that may remain in the body after treatment. PCR can be done with either a bone marrow sample or a blood sample. See *Measurable Residual Disease* on page 27.

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

There are targeted sequencing tests (also called “multigene panels”) that look for specific mutations in the cancer cells. These tests focus on specific sets of genes or areas of DNA. There are also broad DNA sequencing tests (genomic screening tests) that analyze the sequence of large regions of DNA, rather than looking for mutations of specific genes. Doctors may also order sequencing of all the DNA in the cancer cells, and/or normal cells in the body. This test is known as “whole genome sequencing.” The term “next-generation sequencing (NGS)” is a catch-all term that describes a number of different modern sequencing technologies. These technologies allow for sequencing of DNA and RNA much more quickly and cheaply than sequencing methods used previously. In patients with CLL, DNA sequencing is used to look for mutations in the *TP53* and *IGHV* genes.

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

Visit www.LLS.org/booklets to see the free LLS booklets *Understanding Genetics, Cancer Molecular Profiling* and *Measurable Residual Disease* for more information.

Other Blood Tests. Some people with CLL may get the following blood tests before treatment begins:

- **Quantitative Immunoglobulin Test.** People with CLL usually have a weakened immune system and are more vulnerable to infections. Doctors use quantitative immunoglobulin tests to assess a patient's risk of infection. It measures the amount of immunoglobulins in the blood. Immunoglobulins are a type of protein called “antibodies” that are made by B cells in healthy individuals to protect the body from infections. There are three major types of antibodies in the blood: IgG, IgA and IgM. This blood test measures the amount of each type of antibody. Chronic lymphocytic leukemia cells do not make effective antibodies, and they also interfere with the ability of normal lymphocytes to make antibodies. As a result, people with CLL often have low immunoglobulin levels, resulting in immune deficiency and an increased risk of infection.
- **Hepatitis Tests.** Hepatitis is a disease of the liver. It can be caused by the hepatitis C and B viruses. All patients should be tested for hepatitis C because the virus has been associated with B-cell lymphomas. Hepatitis B testing should be performed because some CLL treatments can cause the hepatitis B virus to reactivate.
- **Beta-2 Microglobulin Level.** Beta-2 microglobulin is a small protein found on the surface of many cells, including lymphocytes. It is a marker of how much CLL is in the body.

- **Uric Acid Test.** This test is used to measure the level of uric acid in the blood and assess the patient's risk of developing tumor lysis syndrome (TLS) caused by cancer cells dying quickly.
- **Lactate Dehydrogenase (LDH) Level.** Lactate dehydrogenase is a protein found in most cells. When a cell is damaged, LDH is released into the bloodstream. A high level of LDH in the blood indicates cell damage, and it may also indicate the presence of cancer or other health conditions. When related to CLL, it indicates how much cancer is in the body and how fast it is growing.

Treatment Planning

Choosing a Hospital and a Doctor. When you find out that you have cancer, you want to get the best possible medical care and treatment. So, it is essential to seek treatment in a center with hematologists-oncologists who have significant experience in the care of patients with CLL. A "hematologist" is a doctor who has special training in treating blood disorders. An "oncologist" is a doctor who has special training in treating cancer. A hematologist-oncologist specializes in treating blood cancers.

It is important to discuss all of your treatment options with your doctor to find a treatment that best fits your needs. It is also important to ask questions if there is any information that you do not understand. If time allows, you may want to seek a second opinion from another doctor, as it may help you feel more confident about the recommended treatment plan. The second opinion should come from another hematologist-oncologist, preferably one who treats CLL. This type of doctor will usually have the most knowledge and experience about the latest treatment options for CLL.

If you are unsure about getting a second opinion or feel uncomfortable about how to tell a doctor that you are seeking one, call our Information Specialists at (800) 955-4572 to discuss a way to do so that makes you feel comfortable. You may also want to check with your health insurance company to ensure your plan covers the cost of getting a second opinion.

Fertility. Cancer treatments, including some chemotherapy drugs, radiation and surgery, may affect fertility (the ability to have children in the future). Changes to fertility, which can happen to both males and females, may be temporary or permanent. Before you begin your CLL treatment, it is important to talk with your doctor about whether your treatment could affect your fertility.

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

treatment right away. Even if you must start treatment immediately, a fertility specialist may still be able to help preserve your fertility after you have finished induction therapy and before you continue on with additional intensive post-remission therapies.

Visit www.LLS.org/booklets to see the free LLS booklet *Fertility and Cancer* for more information about fertility preservation.

Prognostic Factors. Certain factors can affect a patient's prognosis—the probable outcome of the patient's cancer. These are called "prognostic factors." Doctors use prognostic factors to help predict how a patient's disease is likely to respond to treatment. These factors help doctors plan the most appropriate initial treatment regimen for each patient. See **Table 4** on page 17 for more information about the CLL International Prognostic Index (CLL-IPI). See **Table 1,** below for prognostic factors for adults with CLL or small lymphocytic lymphoma (SLL).

Table 1. Prognostic Information for CLL/SLL

Method of Detection	Genetic Abnormality	Risk Category
FISH	del(17p)	Unfavorable
	del(11q)	Unfavorable
	+12 (Trisomy 12)	Intermediate
	Normal (no abnormality)	Intermediate
	del(13q) (as a sole abnormality)	Favorable
DNA Sequencing	*TP53*	Wild-type: Favorable Mutated: Unfavorable
	IGHV	>2% mutation: Favorable ≤2% mutation: Unfavorable
Cytogenetic Analysis (Karyotyping)	Complex karyotype (3 or more chromosome abnormalities in more than one cell on karyotype)	Unfavorable

Cytogenetic abnormalities include abnormal changes in the chromosomes and genes of leukemia cells.

Abbreviations: CLL, chronic lymphocytic leukemia; del, deletion; DNA, deoxyribonucleic acid; FISH, fluorescence in situ hybridization; p, the short arm of a chromosome (the upper half); q, the long arm of a chromosome (the lower half); SLL, small lymphocytic lymphoma; +, an extra copy of a chromosome, also known as trisomy.

Sources: Nasnas P, et al. How I Manage Chronic Lymphocytic Leukemia. *Hematology Reports.* 2023; Wan Mohamad Zamri WN, et al. Perspectives on the Application of Cytogenomic Approaches in Chronic Lymphocytic Leukaemia. *Diagnostics (Basel).* 2023

Staging of CLL. When a person is diagnosed with CLL, tests are done to determine the stage of the disease. Staging helps doctors assess how the disease is expected to progress over time and then develop a treatment plan. Staging also helps doctors to determine whether to start treatment right away or delay treatment with regular monitoring to check for disease progression.

Two staging systems, the Rai system and the Binet system, have been used throughout the world in both clinical practice and in clinical-trial settings. In 2016, a prognostic model, the CLL International Prognostic Index (CLL-IPI), was released, allowing for a more targeted management of CLL. In all of the scoring systems, lower numbers or letters indicate a lower level of risk. Higher numbers or letters indicate a higher level of risk.

The Rai and Binet staging systems for CLL are based on the following factors:

- Lymphocytosis (an increase in number of lymphocytes)
- Enlarged lymph nodes, on physical examination
- Enlarged spleen and/or liver, on physical examination
- Anemia (an abnormal decrease in the number of red blood cells)
- Thrombocytopenia (an abnormal decrease in the number of platelets)

The Rai staging system categorizes patients into three separate risk groups, see **Table 2** below.

Table 2. Rai Staging System

Stage	Characteristics	
Stage 0	• Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood	Low Risk
Stage I	• Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood • Enlarged lymph nodes	Intermediate
Stage II	• Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood • Enlarged spleen and/or liver • Enlarged lymph nodes may occur	Intermediate
Stage III	• Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood • Low red blood cell counts (anemia) • Enlarged lymph nodes, enlarged spleen and/or liver may occur	High
Stage IV	• Abnormal increase in the number of lymphocytes in the bone marrow and circulating blood • Low platelet counts (thrombocytopenia) • Enlarged lymph nodes, enlarged spleen and/or liver and anemia may occur	High

Sources: Adapted from Nasnas P, et al. How I Manage Chronic Lymphocytic Leukemia. *Hematology Reports*. 2023; Shadman M. Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Review. *JAMA*. 2023.

The Binet staging system is based on the number of areas of "involved lymph nodes" (defined as lymph nodes larger than 1 cm), the enlargement of the liver and spleen and whether there are reduced numbers of red blood cells and/or platelets. See **Table 3** on page 17.

Table 3. Binet Staging System

Stage	Characteristics
A	• No anemia • No thrombocytopenia • Less than 3 areas of enlarged lymphoid tissue
B	• No anemia • No thrombocytopenia • 3 or more areas of enlarged lymphoid tissue
C	• Anemia and/or thrombocytopenia present • Any number of areas of enlarged lymphoid tissue

Sources: Adapted from Nasnas P, et al. How I Manage Chronic Lymphocytic Leukemia. *Hematology Reports*. 2023.

Although the Rai and Binet staging systems are still widely used, they have certain limitations. These include limited ability to predict which patients will have a more aggressive disease progression, and those with less favorable treatment responses. These staging systems were developed before the discovery of the genetic and chromosomal biomarkers of CLL.

To create a more comprehensive prognostic system, some of these genetic features have been integrated into the CLL-IPI. The CLL-IPI combines the following five prognostic factors to help predict a patient's outlook:

- Deletion 17p and/or *TP53* deleted or mutated = 4 points
- Unmutated *IGHV* = 2 points
- Serum beta-2 microglobulin concentration >3.5 mg/L = 2 points
- Rai stage I - IV or Binet stage B - C = 1 point
- Patient age >65 years = 1 point

Each factor has points—some factors have more points than others. When these points are added up, they provide the patient with a score and a risk group. See **Table 4** below for the CLL-IPI risk groups.

Table 4. CLL International Prognostic Index (CLL-IPI) Categories

CLL-IPI Category	Risk Score
Low Risk	0 - 1
Intermediate Risk	2 - 3
High Risk	4 - 6
Very High Risk	7 - 10

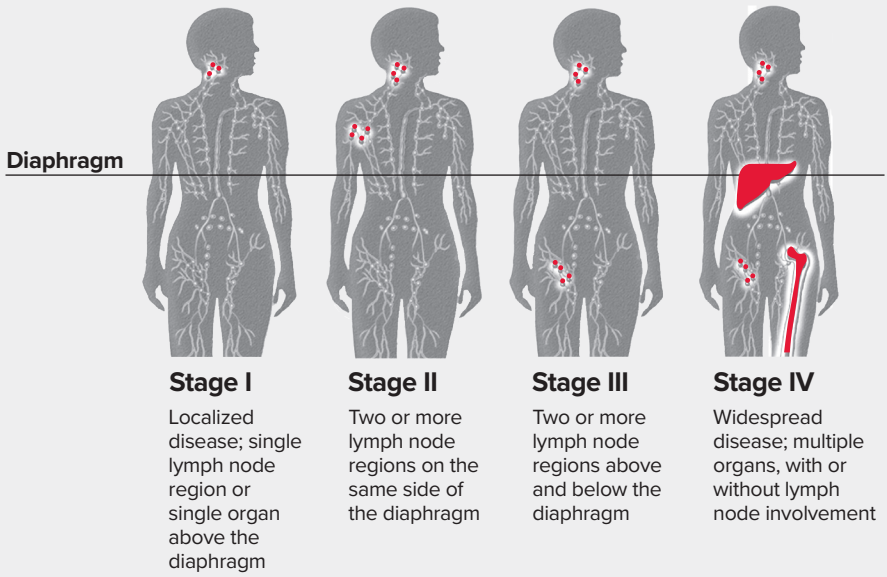
Sources: Adapted from Shadman M. Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Review. *JAMA*. 2023.

Staging of SLL. In staging of lymphoma, the Roman numerals I through IV (1 through 4) are used to represent the extent of cancer in the body. Stage I cancers are less advanced, and patients with stage I cancer often have a better prognosis. Higher-stage cancers are generally more widespread in the body and may require different or more intense treatment. Doctors use the findings from

laboratory and imaging tests to determine the stage. Most people with SLL have disease in their bone marrow, which makes the disease stage IV, but this does not impact the possibility for a complete remission or response to treatment.

The Lugano system, a modification of the older Ann Arbor system, is one of the more widely used staging systems for non-Hodgkin lymphomas (NHLs) such as SLL. See **Figure 3** below for a description of NHL stages.

Figure 3. Non-Hodgkin Lymphoma (NHL) Stages



This illustration shows an example of the location of non-Hodgkin lymphoma in the body for each stage.

Treatment Options

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

Not everyone with CLL receives the same type of treatment. Your doctor will tailor your treatment based on your CLL biomarkers, the stage of your CLL and other factors, such as your age and overall health, as well as your preferences.

Treatment options for CLL have evolved during the last decade. The development of targeted therapies has led to new and more effective treatment regimens, resulting in better patient outcomes. The field of CLL treatment is moving away from chemotherapy to newer targeted therapies. Most people with CLL do very well with newer targeted drugs and immunotherapies. For certain patients, however, chemotherapy remains an important treatment option.

For information about any of the following treatments, please see **Table 8** on page 40.

Targeted Therapy. Targeted therapy uses drugs or other substances to identify and attack specific types of cancer cells and their function but causes less harm to healthy cells. Not all cancers have the same targets. Each type of targeted therapy works slightly differently, but they all interfere with the growth and survival of cancer cells. In most cases, targeted therapies are given orally and are generally better tolerated than chemotherapy agents.

Bruton Tyrosine Kinase (BTK) Inhibitors. Bruton tyrosine kinase inhibitors are long-term therapies—a very different type of approach from chemotherapy. Patients with CLL take these oral medications until they are no longer effective or due to the side effects they are experiencing. Bruton tyrosine kinase inhibitors used to treat CLL include:

- Acalabrutinib (Calquence®)
- Zanubrutinib (Brukinsa®)
- Ibrutinib (Imbruvica®)
- Pirtobrutinib (Jaypirca®)

All BTK inhibitors are associated with increased rates of atrial fibrillation (irregular heart rhythm), hypertension, infection and bruising or bleeding. Patients receiving treatment with a BTK inhibitor who require a surgical procedure should speak with their doctor about stopping the drug for 3 to 7 days before and after the procedure due to the risk of increased bleeding.

Ibrutinib appears to cause more serious side effects (including heart disease) than other BTK inhibitors. For this reason, your doctor may prescribe acalabrutinib and zanubrutinib as first line therapy, which have demonstrated similar efficacy to ibrutinib but have fewer cardiac side effects in clinical trials to date.

Phosphatidylinositol 3-Kinase (PI3K) Inhibitors. Phosphatidylinositol 3-kinase inhibitors include the following drugs:

- Duvelisib (Copiktra®)
- Idelalisib (Zydelig®)

These drugs are not indicated or recommended for first-line treatment. They are associated with higher rates of infection and immune-related side effects. Other possible side effects include diarrhea, rash, fatigue, fever, cough, pneumonia, musculoskeletal pain and anemia.

Symptomatic patients with relapsed CLL are given a PI3K inhibitor, either continuously until it does not work anymore, or they must stop taking it because of the side effects they are experiencing. This drug can cause serious liver function abnormalities and patients should have their liver function monitored with blood tests during the first several months of therapy. In addition, PI3K inhibitors can cause a serious immune-related colitis associated with diarrhea

that often shows up after 9 to 12 months (or longer) on therapy. Patients should tell their doctor if diarrhea develops.

B-Cell Lymphoma 2 (BCL2) Inhibitors. B-cell lymphoma 2 inhibitors include the drug venetoclax (Venclexta®). Treatment with venetoclax can be completed in a set time: 1 year for first-line (initial) treatment and 2 years for relapsed/refractory (previously treated) cases.

Common side effects include low blood cell counts, diarrhea, nausea, upper respiratory tract infection and fatigue. There is a risk of tumor lysis syndrome (TLS), but this can be prevented through appropriate monitoring and prophylactic measures (see *Tumor Lysis Syndrome [TLS]* on page 37).

Monoclonal Antibody Therapy. The following are examples of monoclonal antibodies which bind to CD (cluster of differentiation) 20 proteins on B cells. CD20 is a protein found on the surface of B cells, the cells from which CLL starts.

- Obinutuzumab (Gazyva®)
- Rituximab (Rituxan®)
- Rituximab and hyaluronidase human (Rituxan Hycela®)

In CLL treatment, monoclonal antibodies are usually given in combination with other drugs. Common side effects include fever, chills, nausea, headache, cough, runny nose and shortness of breath.

Chemotherapy. Typically, chemotherapy is given in cycles, with each period of treatment followed by a rest period. There are many types of chemotherapy drugs, including the following antimetabolites and alkylating agents:

Antimetabolite:

- Fludarabine (Fludara®)

Alkylating agents:

- Bendamustine hydrochloride (Bendeka®)
- Chlorambucil (Leukeran®)
- Cyclophosphamide (Cytoxan®)

Chemoimmunotherapy. This type of therapy combines chemotherapy with immunotherapy. Immunotherapy is a type of treatment that uses a person's immune system to help fight cancer.

Rituximab, a type of monoclonal antibody therapy, can be used with chemotherapy to treat CLL. The following regimens use rituximab and chemotherapy to treat CLL:

- FCR: fludarabine, cyclophosphamide and rituximab
- BR: bendamustine and rituximab

Before the introduction of newer targeted agents, younger patients with CLL who needed treatment were given a chemoimmunotherapy regimen, provided they were in good health and had no major comorbidities. The goal of these higher intensity treatments was to induce deep and durable remissions for patients.

Chemotherapy is now less commonly used because there are several available, effective targeted therapies. Chemotherapy is not as effective for CLL with 17p deletion (del) or *TP53* mutation. Currently, first-line chemoimmunotherapy is considered an option for young, fit patients with low-risk disease—patients with mutated *IGHV* but without del(17p) or *TP53* mutations—given the excellent long-term outcomes for these patients.

For more information on these medications, see **Table 7. *Drug Classes and Drug Functions* on page 39 and Table 8, *Some Drugs Used in the Treatment of CLL and SLL* on page 40.**

Radiation Therapy. This treatment uses high-energy rays to destroy cancer cells. It is not part of standard treatment for CLL but is used in rare circumstances to shrink an enlarged spleen, enlarged lymph node masses or masses in locations that interfere with the function of a neighboring body part, such as the kidneys, gastrointestinal tract or throat.

Splenectomy. A splenectomy is an operation to remove the spleen. In some patients, CLL cells can accumulate in the spleen. Sometimes, the spleen becomes so enlarged that it presses on nearby organs, causing discomfort. In rare cases, if other treatments do not help shrink the spleen, the spleen may be surgically removed. This surgery cannot cure CLL, but it can help reduce symptoms. It may also improve blood cell counts and reduce the need for transfusions.

Splenectomy is also used selectively for patients who have severe recurrent bouts of autoimmune diseases that target either the red blood cells (causing autoimmune hemolytic anemia [AIHA]) or the platelets (causing immune thrombocytopenic purpura [ITP]). In such cases, removal of the spleen can help reduce the severity of the anemia (in AIHA) or low platelet count (in ITP). See *Autoimmune Cytopenias* on page 36.

Treatment

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

Treatment Overview. Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all of your treatment options, including clinical trials, you will be taking an active

role in a very important decision that affects you. See *Clinical Trials for Blood Cancers* on page 32.

Talk to your doctor about:

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

In most cases chronic lymphocytic leukemia (CLL) cannot be cured, but there are now many treatment options that have the potential to give patients longer remissions and a better quality of life. Many people with CLL have normal life spans and go long periods without experiencing symptoms or health complications.

People may have treatment for CLL on and off for many years. Speak with your doctor about treatment sequencing. This refers to the determination of the best first-line therapy and the order of additional therapies once treatment begins. Note that current recommendations for this are likely to change as new treatments/drug combinations are approved.

Also, talk to your doctor or healthcare team about the cost of treatment and how long treatment will last. Once these factors are understood, you can begin to plan how to pay for your treatment.

Watch and Wait (Active Surveillance). "Watch and wait" is a treatment approach in which the doctor monitors a patient's condition closely over time and sees the patient for regular check-ups. Active treatment (treatment with drugs or other therapies) is not started until signs and/or symptoms of CLL appear or change. Chronic lymphocytic leukemia is a slow-growing type of leukemia. Most patients with CLL (70% to 80%) do not need treatment when they are diagnosed, and they may not need treatment for several years; however, they will need to be monitored regularly.

At these check-ups, the doctor will:

- Check to see if the patient has developed any new symptoms
- Perform a physical examination to check the size of lymph nodes, spleen, liver, etc
- Order blood tests to determine whether the disease is stable or if it is beginning to progress

During watch and wait, low-risk or intermediate-risk patients may see the doctor every 6 to 12 months while high-risk patients may see the doctor every 3 to 6 months.

During watch and wait, patients are not treated with drugs or other therapies. This is the standard approach for patients with early-stage disease and no symptoms. When people receive a diagnosis of CLL and then learn that they will

not begin treatment right away, they are often concerned. Current research has shown that delaying treatment is safe for many people.

Are you concerned that you will not begin treatment right away? Speak to your doctor to get more information about the watch-and-wait approach.

This approach may seem scary and counterintuitive. Many people who are diagnosed with cancer begin drug treatment right away. But CLL can be a very slow-progressing disease, and in many patients the disease will not be serious enough at the time of diagnosis to warrant drug treatment. In addition, a quarter of patients never need to receive treatment for CLL.

Many studies have compared the watch-and-wait approach to an early-treatment approach for people with low-risk CLL. Studies have led to the following findings:

- To date, clinical trials have not shown any benefits of early treatment in terms of survival.
- Several studies have confirmed that patients with early-stage CLL do not benefit from the use of alkylating agents or aggressive chemotherapy, and these treatments do not prolong survival.
- There are risks associated with early treatment, including potential side effects and treatment complications.
- Patients may develop resistance to the drugs used in early treatment. This means that these drugs are no longer options once disease progression makes treatment essential.

The watch-and-wait approach remains of interest to doctors, and it will continue to be studied in clinical trials.

Visit www.LLS.org/booklets to see the free LLS fact sheet *Watch and Wait* for more information.

When to Start Treatment. Some people with CLL can be managed with a watch-and-wait approach for years before their disease progresses. Treatment is recommended for people whose blood cell counts have gotten worse and have also developed symptoms.

The decision to treat CLL is based on a number of factors that indicate the disease is progressing. According to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines, patients should meet at least one of the following criteria in order to start CLL treatment:

- Bulky lymph nodes
- Bulky liver or spleen

- Presence of specific CLL symptoms
  - Severe fatigue
  - Drenching night sweats
  - Unexplained weight loss of at least 10 percent of body weight within 6 months
  - Fever higher than 100.5° F for 2 or more weeks without evidence of infection
- Doubling of lymphocyte count in less than 6 months, or progressive lymphocytosis with an increase of more than 50 percent over a 2-month period
- A significant decrease in the red blood cell count, due to bone marrow involvement
- A significant decrease in the platelet count, due to bone marrow involvement
- Disease involvement that is extranodal (outside of the lymph nodes) in the skin, kidneys, lungs and spine
- An autoimmune cytopenia that does not respond to treatment with steroids or other therapies. (See *Autoimmune Cytopenias* on page 36)

Testing Before Treatment. Before starting treatment, your doctor should test your cancer cells again for biomarkers (See *Biomarker Testing* on page 10). Biomarkers may change during watch and wait, and the changes may affect treatment decisions. In addition, the doctor will conduct other tests before treatment begins. **Table 5,** on page 25 summarizes the tests that need to be done before a patient begins treatment.

Initial Treatment of Symptomatic CLL. Therapy often begins when patients develop extremely low blood cell counts or when symptoms affect quality of life. It is important that you speak to your healthcare team about the sequence, or order, of your treatments for CLL. Talk to them about long-term treatment versus a fixed-duration treatment and the specific side effects of each treatment option.

Because CLL is more prevalent in older people, evaluation of a patient's fitness and comorbidities (other medical conditions) is very important. Treatment options for CLL are affected by the patient's age, fitness and health.

Another important factor in the treatment choice is the patient's genetic risk profile. For instance, the deletion of the short arm of chromosome 17, abbreviated del(17p), is associated with a less favorable prognosis. The presence or absence of del(17p) is essential information that must be taken into account when determining which treatment option to use. Testing for *IGHV* mutational status is also necessary.

Table 5. Baseline Evaluation of Patients with CLL

Diagnostic Test	General Practice[a]
To establish the diagnosis:	
Complete blood count with differential	Always
Immunophenotyping of peripheral blood lymphocytes	Always
Prior to treatment:	
Medical history and physical exam; performance status[b]	Always
Complete blood count with differential	Always
Bone marrow aspiration and biopsy	When clinically indicated
Serum chemistry, serum immunoglobulin and direct antiglobulin test	Always
Chest x-ray	Always
Infectious disease status	Always
Additional tests prior to treatment:	
Molecular cytogenetics (FISH) test to check for del(13q), del(11q), del(17p) and add(12) in peripheral blood lymphocytes	Always
Conventional karyotyping of peripheral blood lymphocytes (with specific stimulation)	Not generally indicated
TP53 gene mutation	Always
IGHV mutational status	Always
NGS to detect del(17p) or *TP53* gene mutation disruption at a more sensitive level	Possibly
Serum beta-2 microglobulin	Desirable
CT scan of chest, abdomen and pelvis	Not generally indicated
MRI and PET scans	Not generally indicated
Abdominal ultrasound	Possibly

[a]General practice is defined as the use of accepted treatment options for patients with CLL not enrolled in a clinical trial.

[b]Performance status helps to quantify a cancer patient's general well-being and activities of daily life.

Abbreviations: add, addition/extra copy of a chromosome; CLL, chronic lymphocytic leukemia; CT, computed tomography; FISH, fluorescence in situ hybridization; del, deletion or removal of a piece of DNA; MRI, magnetic resonance imaging; PET, positron emission tomography.

Source: Hallek M et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018.

Patients Without del(17p)/*TP53* Mutation. The first, or preferred, treatments prescribed to many patients in this category include acalabrutinib, zanubrutinib or venetoclax in combination with obinutuzumab. Another recommended treatment is ibrutinib. And for patients with *IGHV*-mutated CLL under age 65 years without significant comorbidities, FCR (fludarabine, cyclophosphamide, rituximab) is an option.

Patients who are prescribed a Bruton tyrosine kinase (BTK) inhibitor (acalabrutinib, zanubrutinib, or ibrutinib) will take the drug until it no longer works or until side effects occur that require them to stop taking it. If one BTK inhibitor causes severe side effects, a patient may be able to try a different one. Venetoclax, given in combination with obinutuzumab, is a chemotherapy-free combination and is given for a fixed period of 12 months. See **Table 6** on page 27.

Patients With del(17p) or *TP53* Mutation. Patients with del(17p) or *TP53* mutation (whether younger or older) typically either do not respond well to treatment or are likely to have early relapses if the first-line therapy is any type of chemoimmunotherapy. Treatment with BTK inhibitors, with or without monoclonal antibodies, generally has better results. The following lists suggested treatment regimens for patients with del(17p)/*TP53* mutation.

Suggested Treatment Options for CLL with del(17p)/TP53 Mutation

- **Preferred treatments:**

  Acalabrutinib

  Obinutuzumab

  Venetoclax

  Zanubrutinib

- **Other recommended treatment:**

  Ibrutinib

- For certain patients who can't take BTK inhibitors and venetoclax or who need rapid disease control, using obinutuzumab or high-dose methylprednisolone with either rituximab or obinutuzumab are options.

Clinical trials should always be considered as a treatment option. Allogeneic stem cell transplantation may also be an option for this patient group (see *Allogeneic Stem Cell Transplantation* on page 30).

Table 6. Pros and Cons of Continuous Versus Fixed Duration Treatment

CONTINUOUS THERAPY	FIXED TREATMENT DURATION THERAPY
Pros	**Pros**
• Treatment is given by mouth • Treatment can be taken at home • Some high-risk patients will have control of their disease • Research shows treatment is effective over a long period of time	• Patients develop deep responses • Patients are exposed to limited amount of treatment (via side effects and toxicities) • Potential for re-treatment • Time off treatment • Cost effective
Cons	**Cons**
• Since a patient will be taking this treatment continuously, they are exposed continuously to side effects and toxicities • Treatment may need to stop due to toxicities • Could become resistant to treatment • Cost of treatment	• Weekly dose ramp up of venetoclax may present some practical and logistical burdens

Treatment Outcomes. Patients will be tested to measure whether they have achieved a complete remission. These tests may include a physical examination, blood tests and, sometimes, a bone marrow test and imaging tests. A complete remission is achieved when:

- Blood cell counts return to normal
- Enlarged lymph nodes and organs return to normal size
- Patients no longer have symptoms of leukemia
- The bone marrow shows no evidence of CLL

Measurable Residual Disease. Even when a complete remission is achieved, many leukemia cells that cannot be seen with a microscope may remain in the blood and bone marrow. The presence of these cells is referred to as “measurable residual disease (MRD)” or “minimal residual disease.”

The tests used most often to detect MRD are flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing (NGS). Typically, these three tests use samples of blood or bone marrow cells. The tests are much more sensitive than standard tests that examine cell samples with a microscope.

When patients have less than one CLL cell per 10,000 lymphocytes in blood or bone marrow cell samples based on these sensitive tests, the disease is in a deep state of remission classified as MRD undetectable or MRD-negative. In research studies, patients who remained MRD-negative after completing treatment had better outcomes. An undetectable MRD status after treatment with some drug regimens for CLL is becoming an important factor for predicting prolonged effectiveness of the treatment. In the past decade, MRD assessment has been incorporated into most CLL trials evaluating targeted therapies.

While MRD testing has become widespread in CLL clinical trials, it is not currently part of the routine patient management of CLL. For now, it is not recommended (outside of clinical trials) as part of response evaluation, and it is not used to guide treatment decisions.

Visit www.LLS.org/booklets to see the free LLS fact sheet *Measurable Residual Disease (MRD)* for more information.

Relapsed and Refractory Chronic Lymphocytic Leukemia

Some patients with chronic lymphocytic leukemia (CLL) do not respond to initial therapy. When this occurs, it is called “refractory disease.” In other patients CLL comes back after a remission. In these cases, it is called “relapsed disease.”

Many patients with refractory disease can achieve remission with different treatments, and many patients with relapsed disease can obtain another period of remission with additional treatment. This approach can control CLL for many years. Often people with CLL will require several lines of treatment in their lifetime, and they often have a good quality of life for years after receiving additional treatment. The healthcare team will consider the side effects of medications and tailor the treatment to each individual patient.

Patients should be retested at the time of relapse to determine if their biomarker profile has changed. If someone was treated with a BTK inhibitor that has stopped working, then doctors can evaluate for an acquired BTK mutation. Doctors need this information to plan the next treatment. Once again, in these cases, the healthcare team will consider the side effects of medications and tailor the treatment to each individual patient.

The following general principles are used to guide the sequence of therapy:

- Patients treated with first-line chemoimmunotherapy should be offered targeted therapy, especially if they are in a high-risk category or experienced a short duration of response.

- Patients with intolerance to ibrutinib can be treated with another BTK inhibitor (acalabrutinib, pirtobrutinib, or zanubrutinib).
- Patients whose CLL progresses on a BTK inhibitor can try pirtobrutinib, a novel/noncovalent BTK inhibitor that works a little differently than other BTK inhibitors. Pirtobrutinib may be used when patients become intolerant to other BTK inhibitors.
- The use of PI3K inhibitors should be reserved for patients with CLL that progresses after two or more lines of therapy.
- The use of allogeneic stem cell transplantation should be considered in younger patients (<70 years) with high-risk disease who have had two or more targeted therapies.
- Enrollment in a clinical trial should be considered for patients with progressive disease after several lines of therapy.

The following drugs and combinations can be used for relapsed or refractory CLL:

Preferred treatments:

- Acalabrutinib
- Chimeric antigen receptor (CAR) T-cell therapy with lisocabtagene maraleucel (Breyanzi®) (see page 31)
- Pirtobrutinib
- Venetoclax with obinutuzumab
- Zanubrutinib

Other recommended treatments:

- Allogeneic stem cell transplantation (see page 30)
- Bendamustine with rituximab
- Duvelisib
- FCR (fludarabine, cyclophosphamide and rituximab)
- High-dose methylprednisolone with rituximab or obinutuzumab
- Ibrutinib
- Idelalisib, alone or in combination with rituximab
- Lenalidomide alone or in combination with rituximab
- Obinutuzumab
- Venetoclax
- Venetoclax with ibrutinib
- Venetoclax with rituximab

Acalabrutinib, zanubrutinib, pirtobrutinib, ibrutinib, duvelisib and idelalisib are given for as long as there is a good treatment response, which can be indefinitely. Venetoclax, which is given for a period of 2 years, can be combined with rituximab and, in certain circumstances, obinutuzumab. Patients who have signs of disease progression while they are taking any of these medications should keep taking them until a new therapy is started. Patients should never stop taking their medication unless directed to do so by their doctor.

Patients with relapsed or refractory CLL are advised to speak to their doctors about whether treatment in a clinical trial is a good option. Clinical trials involving new treatments may offer more appropriate treatment options. See *Clinical Trials for Blood Cancers* on page 32.

Allogeneic Stem Cell Transplantation. For some patients who are in remission and can tolerate intensive chemotherapy, the doctor may recommend stem cell transplantation. The goal of stem cell transplantation is to cure the patient's cancer. Typically, the process involves administering intensive chemotherapy, followed by infusion of healthy stem cells from a donor.

This type of transplant is generally recommended to high-risk patients with either deletion of the short arm of chromosome 17 (del[17p]) or *TP53* gene mutation identified early in the course of their disease. It is also considered for those without del(17p) but with relapsed or refractory disease who have been treated with multiple lines of therapy.

Compared to other treatment options, allogeneic stem cell transplantation is associated with a higher rate of side effects and mortality. However, it may be considered for patients with relapsed or refractory CLL categorized as high-risk. The decision to perform an allogeneic transplant also depends on many factors, including the patient's age, physical fitness, comorbidities (other coexisting medical conditions) and social supports (from family members, caregivers, friends, etc), as well as the patient's understanding of the potential benefits and risks.

Allogeneic stem cell transplantation may be an appropriate therapy for carefully selected younger people with CLL who have an available donor. Talk to your doctor to see if this is a treatment option for you.

Reduced-Intensity Allogeneic Stem Cell Transplantation. This type of transplantation may be a treatment option for older patients who cannot tolerate the high doses of chemotherapy used in preparation for a standard allogeneic stem cell transplant. The conditioning therapy in a reduced-intensity transplant uses lower doses of chemotherapy and/or radiation. With a reduced-intensity conditioning regimen, the patient's blood cell counts may not fall as low as they would with high-dose chemotherapy. Additionally, the less

toxic regimens put less strain on the patient's organs, making this regimen safer and more tolerable. This approach is currently under investigation in clinical trials.

Talk to your doctor about stem cell transplantation and ask whether it is a treatment option for you.

Visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information about stem cell transplantation.

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

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

Lisocabtagene maraleucel (Breyanzi®) is FDA (US Food and Drug Administration)-approved CAR T-cell treatment for CLL.

For more comprehensive information, visit www.LLS.org/booklets to see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy.*

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

Clinical Trials for Blood Cancers

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

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

Researchers use cancer clinical trials to study new ways to:

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

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

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

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

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient

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

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

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

Financial Concerns

Patients who have chronic lymphocytic leukemia (CLL) are living longer, primarily because of the development of new and effective drugs. Targeted therapies have improved outcomes for patients with CLL, improving their survival and quality of life. While this progress is exciting, some treatments consist of drugs (used alone and in combination) that require continuous use. There are other CLL drugs that are used for a fixed duration of time. The high cost of cancer treatment can lead to significant financial and emotional stress for both patients and their families. Even if you have health insurance, cancer can still take a toll on your finances. You may have new expenses such as co-payments or travel for treatment. You may also have less income if you need to take time off from work. This can result in financial burden for patients, limited access to medications and lower adherence to treatments.

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

The Leukemia & Lymphoma Society (LLS) offers financial assistance programs to help with insurance premiums, treatment-related co-payments, travel and other expenses for eligible patients. Other organizations also offer financial assistance programs.

You can contact an LLS Information Specialist at (800) 955-4572 for more information about financial assistance programs.

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

Disease and Treatment-Related Complications

Infections. People with CLL may be more susceptible to infections due to the disease itself and/or its treatment. A higher risk of infections is caused by:

- The inability of leukemia cells to make antibodies needed to fight infections
- The effect of treatment, which reduces the number of two types of infection-fighting white blood cells in the blood, called “neutrophils” and “monocytes”

Vaccines. Talk to your doctor about pneumonia, flu, shingles, COVID 19 and any other vaccines. Patients who have CLL should never receive live vaccines, such as Zostavax (a live shingles vaccine), but they can receive an inactivated vaccine, such as Shingrix® (an inactivated shingles vaccine). Patients with CLL have a lower immune response to vaccination compared to the general population and should consider protective measures, such as wearing masks as needed.

Antibiotics and Anti-viral Therapy. Antibiotics are usually required to treat bacterial infections that may occur during the course of the disease. Patients may also receive other drugs to treat viral and fungal infections.

If you get COVID-19, your healthcare team may pause your CLL treatment. Some COVID-19 treatments, such as ritonavir (Paxlovid) can interact with BTK inhibitors and venetoclax.

If you have had a cytomegalovirus (CMV) infection, this virus may be reactivated during CLL treatment with PI3K inhibitors. Rates of reactivation as high as 6 percent have been reported in patients treated with idelalisib. It is important to monitor for this potential problem during idelalisib therapy. Antiviral medications may be given to prevent reactivation of the virus.

Hepatitis B virus (HBV) reactivation has been reported in patients treated with anti-CD20 monoclonal antibody therapy or chemotherapy. Patients treated with acalabrutinib, ibrutinib and idelalisib have also reported HBV reactivation. Reactivation may be prevented with antiviral medications and continuous monitoring for HBV.

For patients with CLL who are undergoing prolonged CLL therapy, aspergillosis can rarely occur. Aspergillosis is an aggressive fungal infection that can

happen when people have a compromised immune system. Aspergillus is a common mold in the environment. There are steps that can be taken to avoid aspergillosis, including avoiding dusty areas, decaying vegetation, dead leaves and close contact to soil or dust.

Please report any changes in your health, memory, or personality to your healthcare team as soon as possible.

Intravenous (IV) Immunoglobulin Replacement Therapy. Some people with CLL do not have enough immunoglobulins (proteins made by B cells that help fight infections). This can lead to repeated lung and/or sinus infections. Immunoglobulin levels can be checked with a blood test. If IgG levels are low, immunoglobulins from donors can be given into a vein through an IV to raise patient levels and help prevent infections. This treatment is often given once a month.

Low Blood Cell Counts. Supportive care for CLL may include administering blood cell growth factors to improve low blood cell counts. The use of white blood cell growth factors may benefit patients who have prolonged low white blood cell counts after treatment. Examples of white blood cell growth factors are:

- Granulocyte-colony stimulating factors (G-CSF), under the names filgrastim (Neupogen®) and pegfilgrastim (Neulasta®), can increase the number of neutrophils
- Granulocyte macrophage-colony stimulating growth factor (GM-CSF) sargramostim (Leukine®) can increase the number of neutrophils and monocytes

Richter Transformation. In about 2 to 10 percent of people with CLL, the disease transforms into a more complex type of blood cancer. The vast majority (90 percent) of this relatively small group of people develop diffuse large B-cell lymphoma (DLBCL), and the other 10 percent develop Hodgkin lymphoma (HL) during the course of their disease and treatment. This complication, known as "Richter transformation" or "Richter's syndrome," is much more common in patients with high-risk factors. These include advanced-stage CLL according to the Rai system; deletion of the short arm of chromosome 17 (del[17p]), trisomy 12, *TP53* or *NOTCH1* mutations; and *IGHV*-unmutated CLL.

Richter transformation generally occurs between 2 and 6 years after a diagnosis of CLL. Patients might suspect Richter transformation if they notice a rapidly or significantly enlarging lymph node, develop B symptoms (i.e., fevers, chills, drenching night sweats or weight loss) or develop a very high lactate dehydrogenase (LDH) level. Lymphocyte masses may also develop in parts of the body other than the lymph nodes. This transformation is more commonly seen in patients who receive chemoimmunotherapy.

Typically, patients with Richter transformation of CLL into DLBCL are treated with chemoimmunotherapy regimens such as RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), BTK inhibitors (acalabrutinib and pirtobrutinib) or regimens designed for DLBCL treatment. Allogeneic stem cell transplantation may be considered following a response to initial therapy. Standard treatment for HL is used for patients with Richter transformation of CLL into HL. With aggressive therapy, these patients tend to do better and may be cured of the lymphoma, although they will not be cured of the underlying CLL.

Some treatment responses have been reported in recent studies with the use of CAR T-cell therapy for patients with CLL with Richter transformation. Treatment in a clinical trial should be considered for these patients. If remission is achieved, these patients should consider an allogeneic stem cell transplant, which is the only curative option.

Call (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials.

Autoimmune Cytopenias. Autoimmune cytopenias are conditions in which the immune system attacks the blood cells. Autoimmune cytopenias occur in 4 to 10 percent of patients with CLL. The most frequent autoimmune cytopenias in patients with CLL are:

- Autoimmune hemolytic anemia (AIHA)
- Immune-mediated thrombocytopenia (also known as “immune thrombocytopenia purpura” or ITP)
- Autoimmune granulocytopenia
- Pure red blood cell aplasia (PRCA)

Autoimmune hemolytic anemia is the most common form of autoimmune cytopenia. People with AIHA produce antibodies that work against their red blood cells, causing them to be eliminated rapidly from the blood. The loss of red blood cells due to these “autoantibodies” can worsen the effects of already low red blood cell counts.

Bone marrow tests may be helpful to confirm the presence of these conditions. The drugs prednisone, rituximab and cyclosporine are sometimes used to treat AIHA and ITP. The drugs romiplostim (Nplate®) and eltrombopag (Promacta®) are both approved by the FDA (U.S. Food and Drug Administration) for the treatment of ITP that is resistant to other treatments. Splenectomy may be considered for treatment of AIHA and ITP in patients who do not respond to drug therapy.

Tumor Flare Reactions. This drug-related complication is a painful enlargement of the lymph nodes that may be accompanied by an elevated lymphocyte count, enlarged spleen, low-grade fever, rashes and bone pain. These reactions are seen in patients with CLL treated with lenalidomide. Use of steroid medications

to control the inflammation and antihistamines to manage the rash are recommended.

Tumor Lysis Syndrome (TLS). This is a potentially life-threatening condition that occurs when large amounts of tumor cells are killed all at once by the cancer therapy, releasing their content into the bloodstream. Patients with very enlarged, "bulky" lymph nodes are considered at high risk for developing TLS (which is best managed if it can be anticipated) and TLS therapy is given before treatment for CLL begins.

Treatment for TLS includes increased hydration, monitoring and management of electrolyte imbalances and abnormal uric acid levels, as well as therapy with the drug rasburicase (Elitek®), as needed. When starting treatment with venetoclax (Venclexta®), it is important to monitor for TLS.

Second Cancer Risk. People with CLL have a high risk of developing a second cancer. This may be due to abnormalities in immune system function that are either associated with the disease or caused by the use of chemotherapy drugs, which can induce potentially long-lasting remission but are also associated with prolonged immunosuppression. The types of cancer that are seen most frequently as a second cancer in patients with CLL are acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), melanoma, gastrointestinal cancer, breast cancer, lung cancer, non-melanoma skin cancer, prostate cancer, kidney cancer, bladder cancer and head and neck cancers.

People diagnosed with CLL can develop AML or MDS whether they receive treatment or not. These complications are more common after treatment with FC (fludarabine and cyclophosphamide) or with FCR (fludarabine, cyclophosphamide and rituximab).

Although all patients with CLL should be advised about their increased risk for developing a second cancer, studies indicate certain factors may help predict increased risk for these other cancers. These factors include:

- Age (higher risk in patients older than 60 years)
- Sex (higher risk in males)

It is important to have follow-up appointments with your hematologist-oncologist on a regular basis due to the increased second cancer risk associated with CLL. An annual comprehensive skin examination is strongly recommended. Sunscreen and skin protection are also highly important.

Follow-up Care

After you achieve a remission, your doctor will continue to monitor your CLL. You will need to continue regular visits to assess your health and blood cell

counts. If indicated, other testing may be required to monitor treatment, as well as to identify signs of disease relapse. You need to keep your treatment team informed of any changes you notice (for example, infections, lymph node changes, etc). These assessments may become less frequent over time.

You are encouraged to:

- Maintain regular follow-up appointments with your hematologist-oncologist. Your doctor will monitor you for signs of disease relapse and you can share any side effects from treatment or the onset of other medical problems.
- Keep a record of your cancer diagnosis, treatment and follow-up care needs. This is often called a "survivorship care plan." Ask your doctor for a written survivorship care plan. Share this information with any new healthcare providers you see. The plan should include the following information:
  - A list of all healthcare providers
  - A diagnosis summary with specifics such as subtype and/or genetic markers
  - A treatment summary with specifics such as the names, dates and dosages of drugs; site of radiation treatment, surgery and/or transplantation information; response to treatment; and side effects
  - Maintenance treatment information, if applicable
  - A list of possible late effects
  - A schedule for ongoing monitoring with recommended tests, frequency and coordinating provider
  - Health and wellness recommendations, such as nutrition guidelines, suggested exercise regimens as well as other appropriate disease screenings
- Receive periodic screening and monitoring for skin, gastrointestinal, kidney, blood, bladder, prostate, breast, lung, head and neck and other types of cancer because of the increased risk of a second cancer associated with CLL (see *Second Cancer Risk* on page 37).
- Seek medical and psychosocial support for fatigue, depression and other long-term effects, if needed.
- Consider cancer risk-reduction strategies, such as smoking cessation, skin protection against prolonged sun exposure, healthy eating and exercising.

For additional survivorship information, visit www.LLS.org/SurvivorshipWorkbook to view the free LLS booklet N*avigating Life During and After a Blood Cancer Diagnosis.*

Drug Information

Table 7, below includes information on drug classifications and their functions and mechanisms of action. **Table 8** on page 40 lists some of the medications used to treat CLL and SLL. For more information, see the package insert and/or the full prescribing information that accompanies each medication available on the internet.

Table 7. Drug Classes and Drug Functions

Alkylating Agents (DNA-Damaging Drugs)	Chemotherapy drugs that prevent cells from reproducing (dividing) by damaging the DNA (deoxyribonucleic acid) in the cells.
Antimetabolites	Chemotherapy drugs that interfere with the normal division and function of cancer cells. Antimetabolites mimic the building blocks of DNA or RNA (ribonucleic acid) that cancer cells need to survive and grow. When the cancer cell uses an antimetabolite instead of the natural substances, it cannot produce normal DNA or RNA and the cell dies.
B-Cell Lymphoma 2 (BCL2) Inhibitors	These drugs inhibit the production of a protein that controls whether a cell lives or dies.
Bruton Tyrosine Kinase (BTK) Inhibitors	These inhibitors help stop growth signals that allow cancer cells to multiply.
Chimeric Antigen Receptor (CAR) T-Cell Therapies	A type of immunotherapy that consists of modifying a patient's own immune cells to recognize and attack cancer cells.
Corticosteroids	Corticosteroids are hormones that can kill lymphocytes. They are believed to work by blocking cell metabolism through their effect on specific genes. In high doses, these synthetic hormones—relatives of the natural hormone cortisol—can kill leukemia cells.
Monoclonal Antibodies	Monoclonal antibodies are laboratory-produced proteins that target specific antigens on the cancer cell's surface to interfere with the cell's function and destroy it. Once the antibody finds and attaches to its target, it can "recruit" (harness) other parts of the immune system to destroy cells that contain the antigen. Monoclonal antibody therapy is a type of immunotherapy.
Phosphatidylinositol 3-Kinase (PI3K) Inhibitors	These drugs block a type of enzyme that transmits signals in cells and that helps control cell growth. Some malignant cells have higher-than-normal levels of PI3K, which causes them to multiply. PI3K inhibitors block the signaling pathways that cause the cancer cells to grow and divide.

Table 8. Some Drugs Used in the Treatment of CLL and SLL

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

Drug Name Administration Type of Drug	Newly Diagnosed	Relapsed/ Refractory
Acalabrutinib (Calquence®) Oral BTK inhibitor	X	X
Bendamustine hydrochloride (Bendeka®) Intravenous (IV) Alkylating agent	X	X
Chlorambucil (Leukeran®) Oral Alkylating agent	X	X
Cyclophosphamide (Cytoxan®) Intravenous (IV) Oral Alkylating agent	X	X
Duvelisib (Copiktra®) Oral PI3K inhibitor		X
Fludarabine (Fludara®) Intravenous (IV) Antimetabolite		X
Ibrutinib (Imbruvica®) Oral BTK inhibitor	X	X
Idelalisib (Zydelig®) Oral PI3K inhibitor		X
Lisocabtagene maraleucel (Breyanzi®) Intravenous (IV) CAR T-Cell Therapy		X
Methylprednisolone Oral Corticosteroid	X	X

Table 8. Some Drugs Used in the Treatment of CLL and SLL (con't)

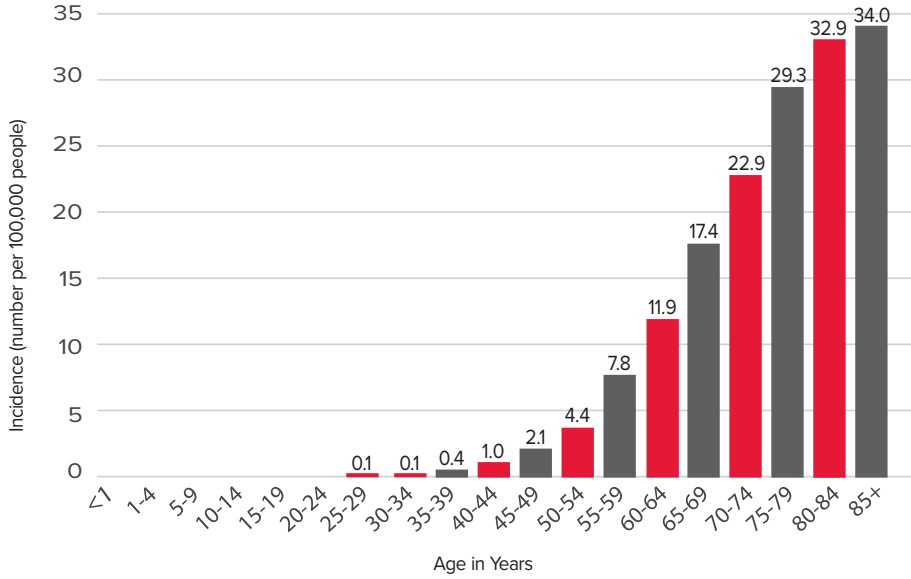
Drug Name Administration Type of Drug	Newly Diagnosed	Relapsed/ Refractory
Obinutuzumab (Gazyva®) Intravenous (IV) Monoclonal antibody	X	
Pirtobrutinib (Jaypirca®) Oral BTK Inhibitor		X
Rituximab (Rituxan®) Intravenous (IV) Monoclonal antibody	X	X
Rituximab and hyaluronidase human (Rituxan Hycela®) Subcutaneous injection Monoclonal antibody	X	X
Venetoclax (Venclexta®) Oral BCL2 inhibitor	X	X
Zanubrutinib (Brukinsa®) Oral BTK inhibitor	X	X

Abbreviations: BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PI3K, phospatidylinositol-3 kinase; SLL, small lymphocytic lymphoma

Incidence, Causes and Risk Factors

Incidence. Approximately 20,700 new cases of CLL were expected to be diagnosed in the United States in 2024. Chronic lymphocytic leukemia is the most common type of leukemia in Western countries, accounting for over 45% of all cases of leukemia. The disease generally affects older individuals (see **Figure 4** below).

Figure 4. Chronic Lymphocytic Leukemia (CLL): Age-Specific Incidence Rates 2016-2020



Source: SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. [updated: 2023 Nov 16; cited 2024 Feb 21]. Available from: https://seer.cancer.gov/statistics-network/explorer/.

Causes and Risk Factors. Although in most cases it is not clear what causes the genetic changes that lead to CLL, there are some known risk factors. 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 never develop a disease, while others with no known risk factors may develop the disease. CLL is not contagious.

The factors that are associated with an increased risk of developing CLL include:

- **Age.** The risk of developing CLL increases with age. The median age at diagnosis is 72 years.
- **Exposure to Certain Chemicals.**
  - Some studies have associated exposure to Agent Orange, an herbicide used during the Vietnam War, with an increased risk of CLL. Veterans who were exposed to Agent Orange may be eligible for additional US

Department of Veteran Affairs (VA) benefits. If you are a Vietnam veteran with CLL, you may want to get a formal evaluation from the VA. Visit www.publichealth.va.gov/exposures/agentorange/ for more information.

- Other studies suggest that exposure to benzene in the workplace increases the risk of CLL. However, the evidence is not as strong for CLL as it is with other blood cancers.

- **Family History.** Genetic factors likely play a role in the development of CLL, as some families have more than one family member with the disease. First-degree relatives of patients with CLL are approximately five to eight times more likely to develop CLL than people who do not have first-degree relatives with the disease. However, the risk is small because the overall chance of getting CLL in a lifetime is low.
- **Sex.** CLL affects more males than females.
- **Race/Ethnicity.** CLL incidence is substantially lower among Asian individuals and higher among Ashkenazi Jews. The reason for these differences is not known.

Visit www.LLS.org/DiseaseRegistries for information on studies about the occurrence of the same type of blood cancer in two or more blood relatives.

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 (B9) 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 5** on page 45.

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

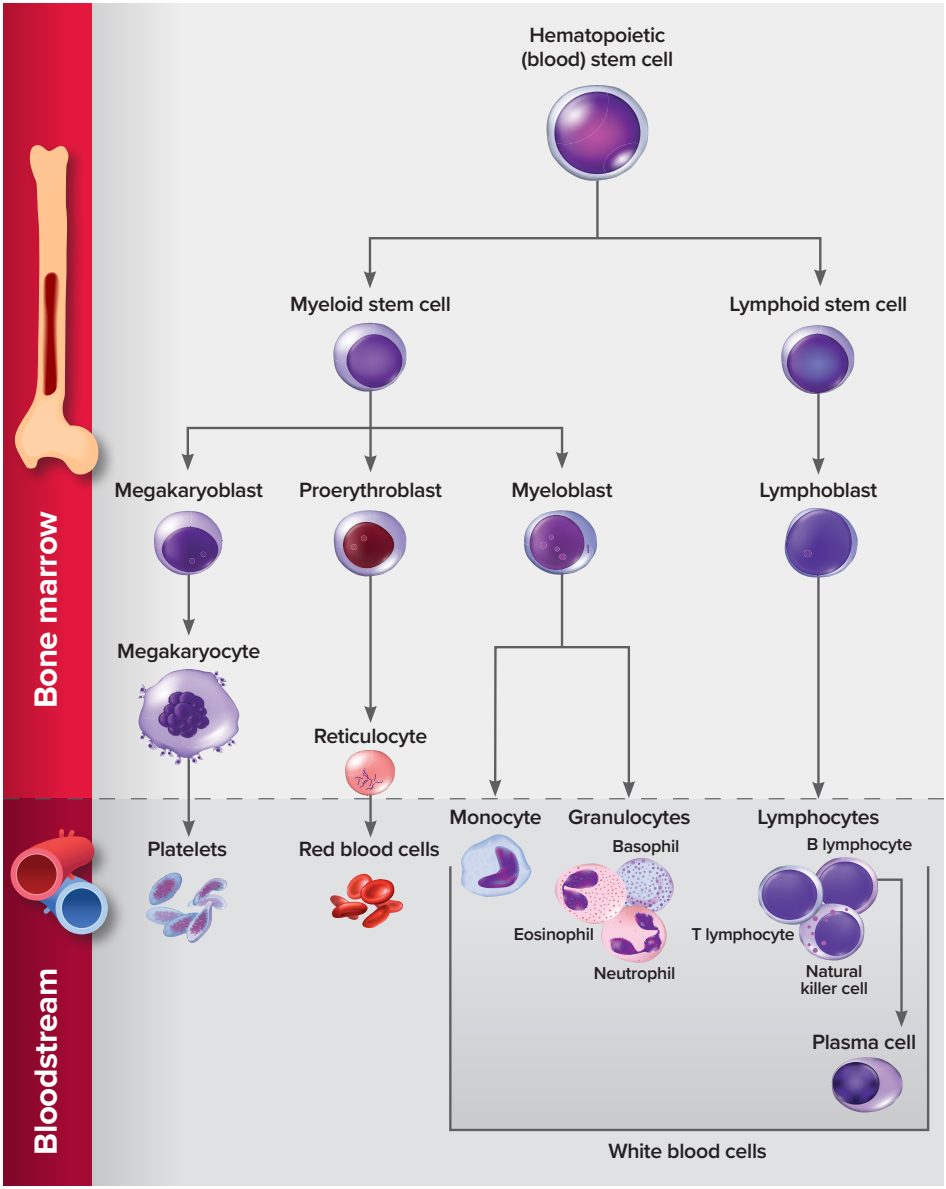
1. Red blood cells (RBCs). These are the cells that carry oxygen.
   - These make up a little less than half of the body's total blood volume.
   - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO_2 is removed from the lungs.
2. Platelets. These are the cells that help blood to 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 (WBCs). These are the cells that fight infections. They include:
   - Neutrophils and monocytes. These cells, called "phagocytes," ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection
   - Eosinophils and basophils. These WBCs respond to allergens or parasites.
   - Lymphocytes. These WBCs, found mostly in the lymph nodes, spleen and lymphatic channels, 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)

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.

Figure 5. Blood Cell & Lymphocyte Development

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



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. A special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

The Lymphatic System

The lymphatic system is the tissues and organs that produce, store and carry lymphocytes (a type of white blood cell) that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). See **Figure 6** on page 47.

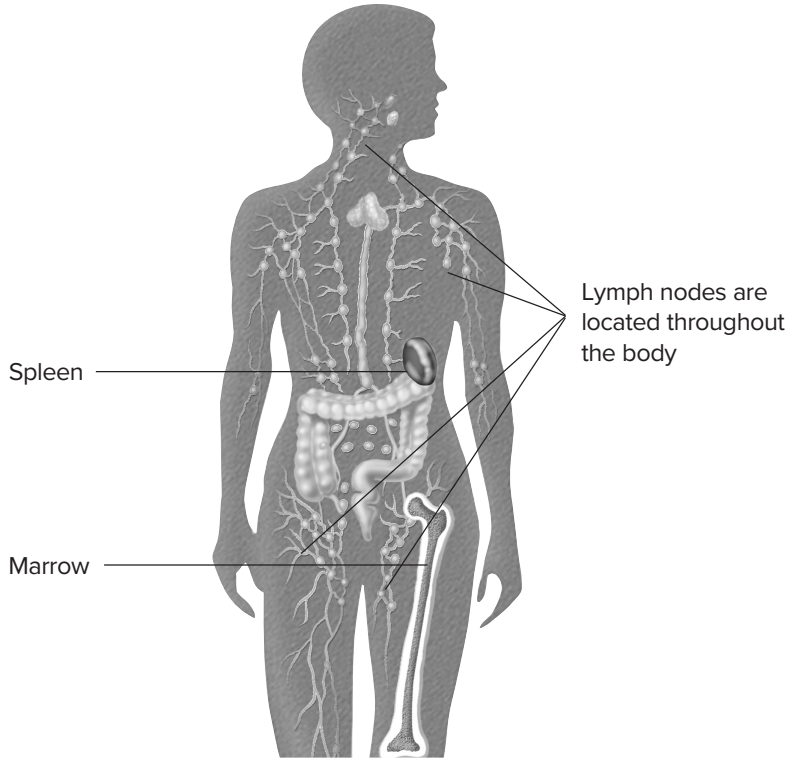
The bone marrow is really two organs in one. It is (1) the organ that forms blood cells, and (2) the organ that forms lymphocytes, which make up part of the immune system.

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

- B lymphocytes (B cells), which make antibodies in response to foreign antigens, especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell (ingest it) along with its attached microbe. The white blood cell then kills and ingests the microbe.
- Natural killer (NK) cells, which attack virus-infected cells or tumor cells without requiring an antibody or other mediation. T cells and NK cells have other functions as well and are important elements in research efforts to design immunotherapies to treat lymphoma and other cancers.

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

Figure 6. The Lymphatic System



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

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

Additional Resources

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

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam; to airborne hazards and burn pits while serving in Iraq, Afghanistan and other areas of Southwest Asia; to contaminated water at Camp Lejeune between 1953-1987; or to ionizing radiation during service may be able to get help from the United States Department of Veterans Affairs (VA). For more information, please

- Call: the VA (800) 749-8387
- Visit: https://www.va.gov/disability/eligibility/hazardous-materials-exposure/

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

Mental Health. Caring for your mental health has benefits for cancer patients. Seek medical advice if you are struggling. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov

If you or your loved one is experiencing a mental health crisis, call 988 to talk to a trained mental health professional. The 988 Suicide and Crisis Lifeline is free, confidential and always available. For the Crisis Text Line, text HOME to 741741.

Other Helpful Organizations. The Leukemia & Lymphoma Society (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, visit www.LLS.org/ResourceDirectory to view the directory.

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

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

For more information, please

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

Health Terms

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

Allogeneic Stem Cell Transplantation. A treatment that uses stem cells from a healthy donor to restore a patient's bone marrow that is damaged or diseased after receiving intensive chemotherapy and/ or radiation therapy. **Visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information.**

Anemia. A condition in which the number of red blood cells is below normal. This results in reduced oxygen flow to the body's organs. Severe anemia can cause a pale complexion, weakness, fatigue, dizziness and shortness of breath.

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. They can also be made in the laboratory and are used to help identify certain types of cancer and also to help treat cancer, either alone or attached to toxic substances.

Antigen. A substance that creates an immune response in the body, 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 their surfaces that can cause an immune response.

Antimetabolite. A type of chemotherapy that interferes with the normal division and functions of cancer cells.

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

Beta-2 microglobulin (B2M). A small protein normally found on the surface of many cells, including lymphocytes, and in small amounts in the blood and urine. High levels of this protein in patients with CLL generally indicate more advanced CLL.

Bone Marrow. A spongy tissue in the hollow central cavity of bones, where blood cells form.

Bone Marrow Aspiration. A procedure in which a liquid sample of bone marrow is removed for examination by a pathologist. The sample is usually taken from the patient's hip bone using a special needle, after a medication

is given to numb the area. Bone marrow aspiration and bone marrow biopsy can be done in a doctor's office or in a hospital and are usually done at the same time.

Bone Marrow Biopsy. A procedure in which a sample of bone containing bone marrow is removed for examination by a pathologist. The sample is usually taken from the hip bone, using a special hollow needle, after medication is given to numb the skin and tissue in that area. Bone marrow aspiration and bone marrow biopsy can be done in a doctor's office or in a hospital and are usually done at the same time.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation.

Chemotherapy. Treatment that stops the growth of cancer cells, either by killing them or 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 so that they will attack cancer cells. The engineered T cells are then multiplied and later reinfused into the patient's bloodstream. **Visit www.LLS.org/booklets to see the free LLS fact sheet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts* for more information.**

Chromosome. Part of a cell that contains genes in a linear order. Human cells have 23 pairs of chromosomes. **Visit www.LLS.org/booklets to see the free LLS booklet *Understanding Genetics* for more information.**

Cluster of Differentiation (CD). A term used along with a number to identify a specific molecule found on the surface of cells that help differentiate one cell type from another. It is commonly used in its abbreviated form, for example, "CD20."

Colony-Stimulating Factor. See Growth Factor

Cytopenia. A condition in which the number of blood cells is lower than normal.

Deletion (del). In genetics, this refers to a portion of a chromosome that is missing.

Eosinophil. A type of white blood cell that is released during infections and allergic reactions.

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.

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 certain genes or chromosomes, they light up when viewed under a specialized "fluorescence" microscope. This test can help to diagnose some types of cancer and plan treatment.

Gene. A small section of DNA that is passed from parent to child. Most genes provide instructions for making specific proteins that are used in one or more types of cells in the body. These proteins perform many important roles in the body, including breaking down food, carrying oxygen and detecting and destroying bacteria and viruses.

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

Growth Factor. A substance made by the body that stimulates the growth of specific cells. Some growth factors are made in the laboratory for use in cancer treatment. For example, granulocyte-colony stimulating factor (G-CSF) is a substance used to increase the number of neutrophils, a type of white blood cell.

Hematologist. A doctor who specializes in blood cell diseases. A "hematologist-oncologist" specializes in blood cancers.

Hematopoiesis. The formation of all types of blood cells that starts in the bone marrow. For the blood cell development process, see *Normal Blood and Bone Marrow* on page 43.

Hemoglobin. A protein inside red blood cells that carries oxygen around the body. Hemoglobin concentration decreases when there is a drop in the number of red blood cells.

Imaging Test. A type of test that makes detailed pictures of areas inside the body. Imaging tests use different forms of energy such as x-rays, ultrasound and radio waves.

Immunoglobulin. A protein made by B cells and plasma cells that helps the body fight infection.

Immunophenotyping. A process used to find specific types of cells within a blood sample. It looks at antigens or markers on the surface of the cells to identify antibodies.

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

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

Lymphatic System. The tissues and organs that produce, store and carry white blood cells that fight infections and other diseases. This system includes the lymph nodes, the spleen, thymus and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells).

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

Lymphocytosis. An elevated number of lymphocytes in the blood. Technically, all patients with CLL have lymphocytosis at the time of diagnosis, but small lymphocytic lymphoma (SLL) patients may not. Some patients treated with BTK inhibitors may also have an increase in the number of lymphocytes in the blood that occurs soon after the therapy is started.

Macrophage. A type of white blood cell, referred to as a "scavenger cell," that surrounds and kills microorganisms, removes dead cells and stimulates the action of other immune system cells. See Monocyte

Measurable Residual Disease (MRD). The small amount of cancer cells that may remain in the body after treatment, even when the patient's blood and bone marrow may appear to be normal. These residual cancer cells cannot be seen under a microscope and can only be identified by other very sensitive tests like polymerase chain reaction (PCR), next-generation sequencing (NGS) or flow cytometry. Also called "minimal residual disease." **Visit www.LLS.org/booklets to see the free LLS fact sheet *Measurable Residual Disease (MRD)* for more information.**

Monocyte. A type of white blood cell that is made in the bone marrow and travels through the blood to tissues in the body, where it becomes a macrophage. See Macrophage.

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. An abnormal decrease in the number of neutrophils, a type of white blood cell, in the blood. People with low neutrophil counts are susceptible to infections.

Neutrophil. A type of white blood cell, and the principal type of phagocyte (microbe-eating cell), in the blood. It is the main type of cell that combats infection.

Next-Generation Sequencing (NGS). This refers to a number of different gene sequencing technologies that can rapidly examine stretches of DNA or RNA (ribonucleic acid).

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

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

Oral Medication. Treatment with drugs taken by mouth.

Pathologist. A doctor who has special training in identifying diseases by examining cells and tissue samples under a microscope.

Performance Status. A measure of how well a person is able to perform ordinary tasks and carry out daily activities.

Peripheral Blood. The blood that circulates throughout the body in the arteries, capillaries and veins.

PET Scan. A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is taken up. Because cancer cells often take up more glucose than normal cells, the pictures can be used to find cancer cells in the body.

Platelet. A small, colorless piece of a cell that helps control bleeding. Platelets are produced from large cells in the bone marrow, called "megakaryocytes." Platelets travel to and then collect at the site of a wound. The platelets' sticky surface helps them form clots at the site of the wound and stop bleeding. Also called "thrombocyte."

Polymerase Chain Reaction (PCR). A very sensitive laboratory genetic test that is used to detect and measure some genetic mutations and chromosomal changes that cannot be seen with a microscope. It essentially amplifies (increases) small amounts of specific pieces of either DNA or RNA so that they are easier to detect and measure. This test can find a single cancer cell among more than approximately 100,000 healthy blood cells.

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

Reduced-Intensity Stem Cell Transplantation. A type of allogeneic stem cell transplantation in which patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. The chemotherapy and radiation do not completely kill all the leukemia cells, but the new immune cells that the patient receives in the transplant may attack the leukemia cells. This protocol may be safer than a traditional high-dose conditioning or "myeloablative" allogeneic stem cell transplant, especially for older patients. **Visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information.**

Refractory. The term used to describe a disease that does not go into remission or improve substantially after treatment.

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

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

Resistance to Treatment. When cancer cells continue to grow even after administration of strong drugs and/or treatments, the disease is said to be "treatment resistant."

Richter Transformation. A rare condition in which CLL changes into a fast-growing type of lymphoma.

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." Surgical removal of the spleen is known as "splenectomy."

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation.

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.

Subcutaneous Injection. The administration of medication with a needle that goes under the skin into the space between the skin and muscle.

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

White Blood Cell. A type of 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."

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

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

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

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

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

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The mission of The Leukemia & Lymphoma Society (LLS) is to cure blood cancer and improve the quality of life of all patients and their families. Find out more at www.LLS.org.

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