NCCN GUIDELINES FOR PATIENTS®

2025

Chronic Lymphocytic Leukemia

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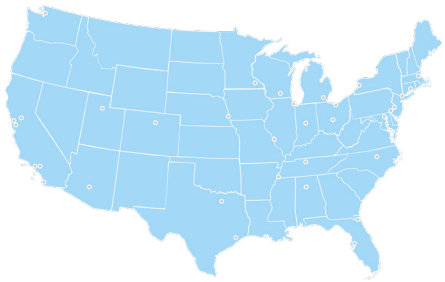
About the NCCN Guidelines for Patients®

National Comprehensive Cancer Network®



Did you know that top cancer centers across the United States work together to improve cancer care? This alliance of leading cancer centers is called the National Comprehensive Cancer Network® (NCCN®).

Cancer care is always changing. NCCN develops evidence-based cancer care recommendations used by health care providers worldwide. These frequently updated recommendations are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The NCCN Guidelines for Patients plainly explain these expert recommendations for people with cancer and caregivers.

These NCCN Guidelines for Patients are based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2025 – October 1, 2024.

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NCCN Foundation seeks to support the millions of patients and their families affected by a cancer diagnosis by funding and distributing NCCN Guidelines for Patients. NCCN Foundation is also committed to advancing cancer treatment by funding the nation's promising doctors at the center of innovation in cancer research. For more details and the full library of patient and caregiver resources, visit NCCN.org/patients.

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About CLL

Chronic lymphocytic leukemia (CLL) is a type of blood cancer. It grows slowly. Treatment may not be needed for years. Some patients may never need treatment. However, for the majority of patients who do, newer treatments can help extend life.

What is CLL?

CLL stands for:

- **Chronic** – a condition that doesn't go away
- **Lymphocytic** – occurs in the lymphocytes, a type of white blood cell
- **Leukemia** – cancer that occurs in blood cells

Put together, chronic lymphocytic leukemia is a condition in your lymphocytes that doesn't go away. It's considered a form of cancer.

Your blood contains several types of blood cells. One of those is white blood cells.

B cells, also called B lymphocytes, are one type of white blood cell. They're made within the soft, spongy tissue inside most of your bones called bone marrow. When they've matured properly, B cells leave your bone marrow to work in your bloodstream.

Why you should read this book

Making decisions about cancer care can be stressful. You may need to make tough decisions under pressure about complex choices.

The NCCN Guidelines for Patients are trusted by patients and providers. They clearly explain current care recommendations made by respected experts in the field. Recommendations are based on the latest research and practices at leading cancer centers.

Cancer care is not the same for everyone. By following expert recommendations for your situation, you are more likely to improve your care and have better outcomes as a result. Use this book as your guide to find the information you need to make important decisions.

In people with CLL, abnormal B cells grow out of control, crowding out healthy B cells.

This oversupply of abnormal B cells prevents healthy B cells from performing their duties effectively. This results in fewer healthy blood cells and a higher risk of infection.

What are the symptoms of CLL?

Usually, CLL doesn't cause symptoms at first. It may be found due to routine blood testing.

Symptoms of CLL may include the following. See a health care professional as soon as you can if you have any of these symptoms:

- Swollen glands in your neck, or you feel swelling in your stomach
- Feel tired more easily or fatigue
- Excessive sweating or night sweats
- Fever
- Infections that keep coming back despite treatment
- Loss of appetite or becoming full too quickly (early satiety)
- Unintentional weight loss

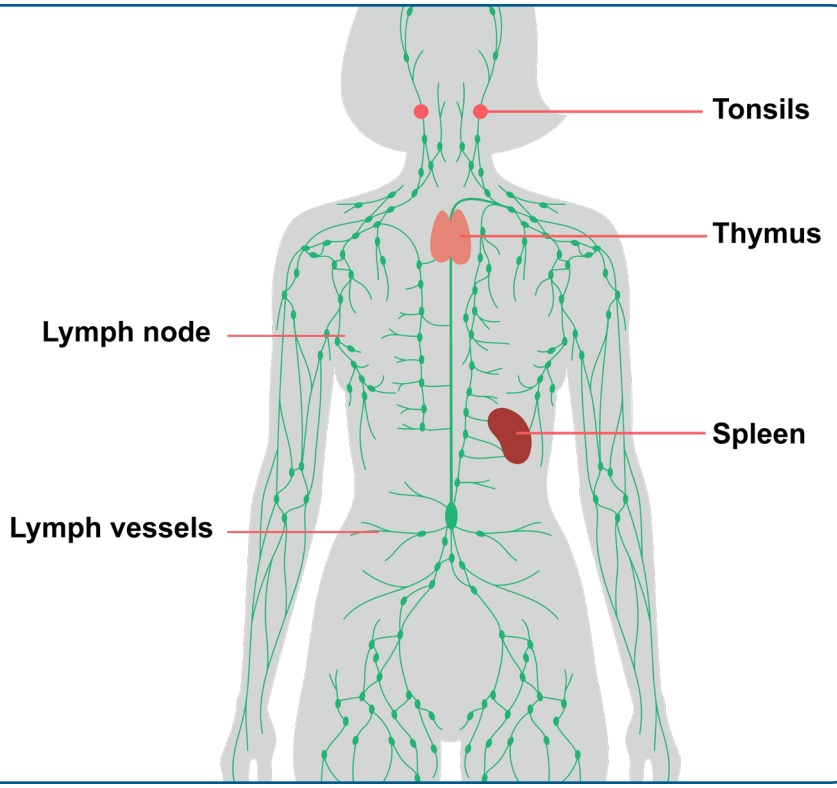
What causes CLL?

The specific cause of CLL isn't currently known other than that there is a change within the bone marrow. It can be tied to several factors:

- Older adults tend to develop changes or mutations that could cause cancer like CLL to form over time
- Blood relatives of someone with CLL can have a higher chance of getting CLL themselves

Lymph system

Many B cells are in the lymph (or lymphatic) system. This system plays a key role in fighting infections. The tonsils, thymus, spleen, and lymph vessels and nodes are parts of the lymph system (shown). There are hundreds of lymph nodes in the body, and many are in the neck, armpits, and groin.



How is CLL treated?

Treatment of CLL depends on your body. You may not need treatment right away. But treatment may be needed if your white blood cell count is rising rapidly, if you have low numbers of other normal blood cells (anemia, low platelets, or low neutrophils), if you have large or uncomfortable lymph nodes, or if you have symptoms listed above.

Many treatment options are available and should be discussed with your doctor at your first visit and as your condition is followed. These range from pills you take every day to a combination of IV infusions and pills taken for a specific amount of time.

You may live for years without needing treatment. If or when someone needs treatment can vary greatly from person to person.

You may have a more intense or aggressive treatment plan if you develop Richter transformation, which is described later. This rare condition can lead to a more aggressive cancer called diffuse large B-cell lymphoma (DLBCL) or another cancer called Hodgkin lymphoma.

Is there a cure for CLL?

There is currently no cure for CLL, but you can get effective treatment so your blood cells will be mostly healthy ones and a full life is possible. This is a condition called minimal residual disease. We'll describe this in a later chapter.

While the goal of treatment is not to cure CLL, the goal is to prevent the disease from causing problems and from becoming life-threatening.

What is SLL?

Small lymphocytic lymphoma, or SLL, is the same cancer as CLL. The only difference between the two is where the abnormal cells are found.

CLL is mostly found in the blood and bone marrow. SLL is mostly found in lymph nodes and the spleen. If a person has fewer than 5,000 cancerous cells in their blood, it is considered SLL. Anything more than that is considered CLL.

The lymph nodes and spleen play a key role in fighting infections.

CLL can also be found in the lymph nodes. Lymph nodes and the spleen may be swollen because of a buildup of CLL or SLL cells.

Treatment of CLL and SLL is the same because the cancer cells are the same. For this book, treat any recommendation for CLL as one for SLL. For this reason, the disease is often referred to as CLL/SLL.

What can you do to get the best care?

Advocate for yourself. You have an important role to play in your care. In fact, you're more likely to get the care you want by asking questions and making shared decisions with your care team.

The NCCN Guidelines for Patients will help you understand cancer care. With better understanding, you'll be more prepared to discuss your care with your team and share your concerns. Many people feel more satisfied and less anxious when they play an active role in their care.

You may not know what to ask your care team. That's common. Each chapter in this book ends with an important section called *Questions to ask*. These suggested questions will help you get more information on all aspects of your care.

Take the next step and keep reading to learn what is the best care for you!

What's in this book?

This patient guide describes everything you need to know about living with CLL, including:

- Tests needed to determine the best treatment for you
- A period of monitoring, known as "watch and wait"
- Treatments available for CLL
- Caring for a rare complication called Richter transformation
- Supportive care to improve your quality of life

2
Testing for CLL

You'll need specific tests to confirm you have chronic lymphocytic leukemia (CLL). If CLL is found, you'll need more tests to decide when to start treatment, which treatment will work best, and what supportive care you'll need.

How is CLL confirmed?

Chronic lymphocytic leukemia (CLL) is confirmed with a blood test.

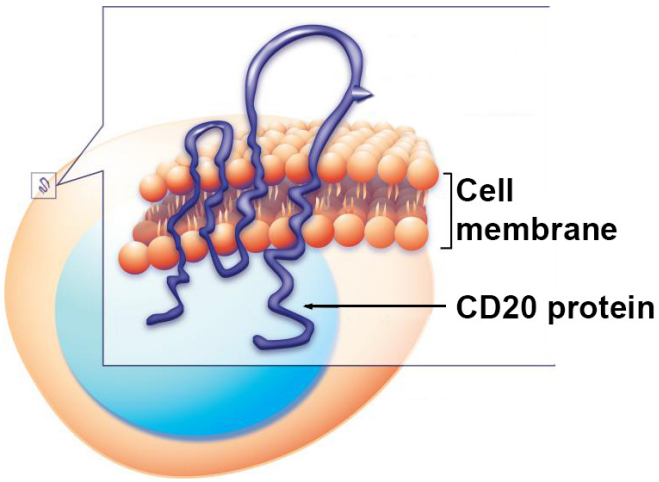
Diagnosis by blood tests

You'll have a blood test where you'll provide a small sample of your blood, which will be sent to a lab for testing.

A specialist called a hematopathologist is an expert at diagnosing cancers of blood and immune cells. They look at blood, bone

Immunophenotype

Chronic lymphocytic leukemia (CLL) often has a common pattern of surface proteins on its cells. An example of these proteins is CD20 (shown). It helps identify the correct type of cancer. For instance, CLL cells have proteins called CD200 and LEF1, but another type of lymphoma, called mantle cell lymphoma, does not have them.



marrow, and lymph node samples for signs of disease.

The hematopathologist and your oncologist will examine a drop of your blood using a microscope. This is called a blood smear. The way the abnormal cells look can be a clue as to what type of cancer you have.

Your blood will also be tested using a method called flow cytometry. It can detect common patterns of proteins on the outside of cells. Most cells have an identifiable pattern of proteins, like a silhouette or a shape, called the immunophenotype.

A CLL diagnosis requires at least 5,000 or more of the same white blood cells called monoclonal B lymphocytes to be found per microliter in your blood.

Diagnosis by biopsy

A biopsy is a procedure that removes samples from the body for testing. If the blood results aren't clear, you'll have a biopsy of your lymph nodes or bone marrow to confirm CLL. Tests of lymph nodes will also confirm small lymphocytic lymphoma (SLL).

An excisional biopsy is when a whole lymph node is removed by a surgeon, while an incisional biopsy removes only part of a lymph node.

There are many lymph nodes throughout your body, so if you have a lymph node removed, you won't lose your ability to fight infections and disease.

Needle biopsies take a small sample of a lymph node using a needle. They can be done when other biopsies are not safe to perform.

A lab test will be used to find the immunophenotype of the biopsied cells.

A bone marrow biopsy removes a core sample of marrow. A bone marrow aspiration removes liquid and cells from the marrow. These procedures are usually done at the same time. They're performed on the back of the hip bone.

You may receive an injected pain blocker or light sedative to help you relax. Tests of bone marrow aren't usually needed for diagnosis, so you might not get one.

How is treatment planned?

Lab results used for diagnosis are included in a report. This report will be sent to your hematologist-oncologist, an expert in blood cancers. You may be able to view the pathology report using an online patient portal, or you could ask for a copy.

The report is used to plan your treatment. Your oncologist will review the results with you. Take notes and ask questions.

What tests are needed for starting treatment?

The tests used to provide care are listed in **Guide 1** and are described next.

Health history

Expect your care team to review your health in detail. This is known as taking a medical history. They will want to know a lot about your past and current health. You will likely be asked about:

- Family history
- Illnesses, infections, and injuries

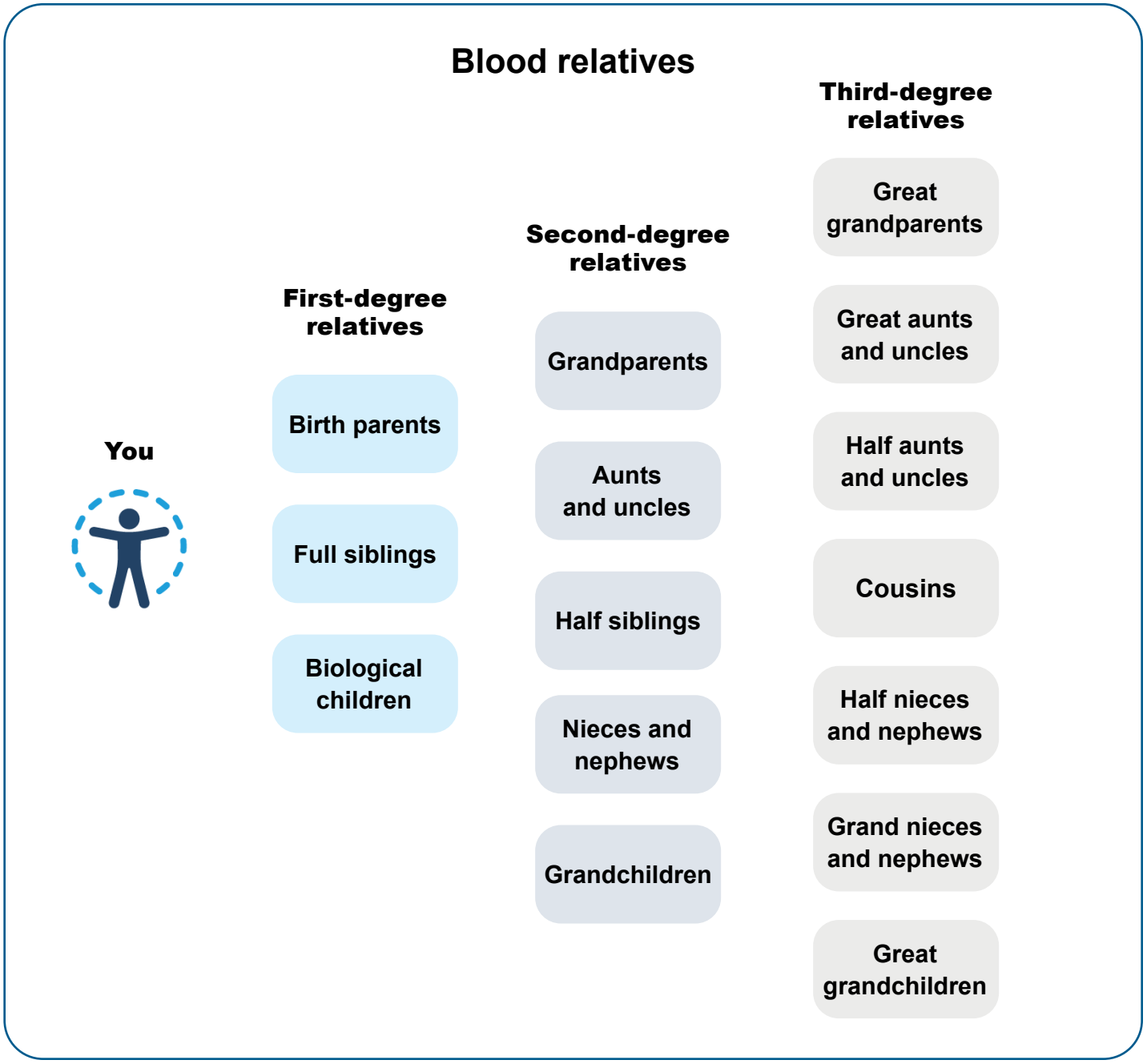
Guide 1
Tests used to plan treatment of CLL

Tests that are needed for planning	• Medical history including B symptoms and family history • Physical exam including lymph nodes, spleen, and liver • Performance status score • Flow cytometry • Complete blood count (CBC) with differential • Comprehensive metabolic panel • Beta-2 microglobulin • FISH, DNA sequencing, and CpG-stimulated karyotype
Tests that may be useful for planning, but not needed	• LDH • Quantitative immunoglobulins • Reticulocyte count, haptoglobin, and direct antiglobulin (Coombs) test • Uric acid • Hepatitis B and hepatitis C test • Bone marrow biopsy and aspirate • Diagnostic CT scans of chest, abdomen, and pelvis • Pregnancy test

- Prescription and over-the-counter medicines and supplements, surgeries, and blood transfusions
- Lifestyle choices, like your diet, how active you are, and whether you smoke cigarettes or drink alcohol

They'll also ask if you're having any symptoms and complications of CLL. These symptoms are called B symptoms and include:

- Fevers when you're not sick
- Night sweats that drench your sheets
- Weight loss you didn't expect



Some cancers and other health problems can run in families. Be prepared to discuss the health of your close blood relatives, like your siblings, parents, and grandparents. These are your first- and second-degree relatives, as seen in the figure below. Relatives are 7 to 8 times more likely to develop CLL if there's a family history.

Physical exam

Your hematologist/oncologist will perform a physical exam of your body. This exam will include:

- Checking your vital signs—blood pressure, heart rate, breathing rate, and body temperature—and assessing your overall appearance
- Feeling and listening to organs
- Assessing your level of pain, if any, when you are touched

Checking for swelling

Cancer cells can build up in lymph nodes, the spleen, and the liver causing them to swell. Your oncologist will look at and gently press on your body to assess their size. Areas that may be touched include your neck, armpit, belly, and groin.

Performance status

Performance status is your ability to do daily activities, like feeding yourself or bathing. Your oncologist will score your performance status based on your health history and exam.

Blood tests

Blood tests can measure blood cells, proteins, and chemicals in the bloodstream. If you haven't had a blood test recently, you'll get a complete blood count (CBC) with differential.

- A CBC measures parts of the blood including counts of white blood cells, red blood cells, and platelets.
- A differential counts the most common types of white blood cells in your blood. It also checks if the cell counts are in balance with each other.

White blood cell counts are often high at diagnosis of CLL. Other blood counts, such as red blood cells or platelets, may be low.

A comprehensive metabolic panel is a screening test for many diseases. It often includes tests for up to 14 chemicals in the blood. Abnormal levels may mean your kidneys and liver are not working as they should.

Beta-2 microglobulin is a small protein found on most cells. It is released by cells into the blood by B cells. High levels of beta-2 microglobulin may suggest CLL is growing.

Bone marrow tests

Bone marrow tests are not often needed to diagnose CLL. However, they may be done to find out what's causing low blood cell counts.

Biomarker tests

CLL cells have unique features that can be used to plan treatment specifically for you. These features are called biomarkers.

Biomarkers are found with lab tests using either a blood or bone marrow sample:

- Fluorescence in situ hybridization (FISH) can show missing parts and extra copies

of genetic material called chromosomes. It can detect a biomarker called 17p deletion.

- DNA sequencing is used to look for mutations in the *TP53* and *IGHV* genes, which control how your cells die when they're not healthy.
- A karyotype can show defects in chromosomes. A complex karyotype is 3 or more unrelated changes or deletions in more than one cell.

Biomarkers used to select treatment are discussed in *Chapter 4: Treatment for CLL*.

Diagnostic CT

Computed tomography, or CT, is like an x-ray but it shows body tissue more clearly. A diagnostic CT uses more radiation than regular CT and adds a contrast agent. Some people refer to this as a CAT scan.

A contrast agent is a chemical that highlights body tissues for the scanner. It's given to you through a needle placed into a vein in your arm. Some people can't have contrast due to certain health issues, like allergies or chronic kidney disease. Ask if contrast is safe for you.

A diagnostic CT of your chest, abdomen, and pelvis may be needed for 2 reasons:

- To look for big lymph nodes that may be causing symptoms
- To assess the extent of the cancer before starting treatment

Since a CT scan is often not needed, you should ask your doctor what the reason is to obtain the test.

A CT scan is done in the radiology department, in a big machine that looks like a tunnel. The scan won't hurt, but if you need contrast you will need to get a needle placed in your arm.

A radiologist will review your scans and send the results to your oncologist.

"I am so grateful I had a consultation with a CLL specialist. It was reassuring to finally speak to a CLL specialist. The doctor answered all my questions thoroughly. I am very satisfied with the advice I received."

What if I’m pregnant?

Some cancer treatments can harm an unborn baby. If you have the potential to become pregnant, your cancer care team will give you a pregnancy test before treatment.

Your treatment options will depend on the results.

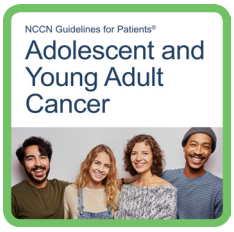
Preserving fertility

Many people have healthy babies despite cancer and its treatment. If you wish to have kids, there are important steps to take before treatment. Even if you are unsure, talk to your cancer care team.

Fertility is the ability to have a baby. Some cancer treatments can damage the body parts needed for fertility. Ask your care team if you’re at risk for impaired fertility. It can happen to people of any gender.

You may receive a referral to a fertility specialist. A fertility specialist is an expert in helping people have babies. They can explain how you may be able to have a baby during or after treatment. Collecting and freezing sperm or eggs is a common method.

More information on fertility preservation can be found in the *NCCN Guidelines for Patients®: Adolescent and Young Adult Cancer,* available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Cancer treatment can impact one's ability to have children. Before starting treatment, talk with a fertility counselor to learn what your options are for fertility preservation.

What's a prognosis?

Prognosis is the likely course and outcome of a disease based on tests. Prognosis is used to predict how the cancer will turn out.

Some people with CLL want to know the prognosis, but others don't. Tell your care team what information you do and do not want to know.

Some people with CLL have certain biomarkers that can be targets for chemoimmunotherapy. More research is needed to know how they predict the results of targeted therapy. **See Guide 2.**

Beta-2 microglobulin is also a biomarker used to determine how hard cancer will be to treat. High levels may suggest that CLL will likely be harder to treat.

What's next?

What happens next depends on what your tests find. You may move on to a stage called "watch and wait". This means you won't start any treatment aside from those that make you feel better if you're sick. We'll talk about this ~~it~~ more in Chapter 3: Watch and wait.

You could move on to treatment right away if your care team feels you need to. We'll tell you all about what treatments you could use in *Chapter 4: Treatment for CLL.*

There's a condition called Richter transformation that we describe in Chapter 5: Richter transformation. If your care team tells you that you have this, we advise you to read that chapter.

Guide 2
Treatment outlook based on CLL biomarkers

Biomarkers	Outlook
13q deletion, unmutated *TP53*, mutated *IGHV*	Favorable
Trisomy 12, normal chromosomes	Average
11q deletion, 17p deletion, *TP53* mutation, unmutated *IGHV*, or having more than one mutation or deletion (complex karyotype)	Unfavorable

Key points

- A diagnosis of chronic lymphocytic leukemia (CLL) is most often made with blood tests.
- To plan treatment, your care team will find out your health history and examine your body. Blood tests will be done to learn if CLL is growing and affecting organs.
- More blood tests may be done to check for serious health problems caused by CLL. Some people will need bone marrow tests or imaging.
- If you can get pregnant, your care team will give you a pregnancy test.
- Ask your care team if you are at risk for impaired fertility. There are ways to have a healthy baby after cancer treatment.
- Your care team may plan care based on the likely outcome of your cancer, called the prognosis.

Questions to ask

- Will my insurance pay for all of the tests you are recommending?
- Do I need to do anything to prepare for testing?
- How soon will I know the results and who will explain them to me?
- How can I get a copy of the pathology report and other test results?

3
Watch and wait

Chronic lymphocytic leukemia (CLL) isn't always treated right away. Your care team will check the cancer often and start treatment when it's needed. This approach is called watch and wait.

What is watch and wait?

Watch and wait is a period of testing for changes in your condition. It can go on for years. Your care team may call it observation, active surveillance, or watchful waiting.

Some people call this period "watch and worry," but your worry should fade over time. During watch and wait, your care team will monitor your symptoms and blood counts.

Meanwhile, you can take care of your health in several ways:

- First, go to your health appointments. Don't skip or delay them.
- Second, find support. Watch and wait can cause worry or anxiety. Support groups or professional support may be helpful.
- Third, live a healthy lifestyle to improve your overall health.

See Chapter 6: Supportive care for information to help you during watch and wait. This chapter explains recommendations for vaccines and care for cancer symptoms. It also describes other NCCN resources that can help improve your quality of life.

Will I be okay without treatment?

You may start treatment for chronic lymphocytic leukemia (CLL) months or years after diagnosis. Or you may never need treatment.

Unlike other cancers, CLL grows very slowly. A term your care team might use is "indolent" (pronounced IN-doe-lint). Cancer that's indolent moves very slowly.

Current research shows that delaying treatment is safe for many people. There's research being done to find out whether treatment should be delayed or started sooner.

Reasons to delay treatment include:

- Treating CLL early does not help you live longer.
- Treatment may cause unwanted health problems called side effects which are inconvenient and may have out-of-pocket costs.
- There may be better treatments available in the future.
- Treatment may never be required at all.

You can enroll in a clinical trial that assesses if early treatment is helpful.

When does treatment begin?

You won't start treatment until the blood tests have been done. Your cancer care team will use staging to figure out where you are in your treatment journey.

Rai stages

The Rai staging system is commonly used for CLL. The Binet staging system is another staging system used for CLL. The Rai and Binet systems are often used together.

The Rai system consists of 5 cancer stages ranging from stage 0 to stage 4. The criteria for each stage are listed in **Guide 3.**

The 5 stages can be condensed into three risk groups:

- Stage 0 has a low risk of needing treatment soon.
- Stages 1 and 2 have an intermediate risk of needing treatment soon.
- Stages 3 and 4 have a high risk of needing treatment soon. Treatment is typically started within weeks to a few months.

Guide 3
Criteria for Rai stages of CLL

	Rai stage 0	Rai stage 1	Rai stage 2	Rai stage 3	Rai stage 4
Many CLL lymphocytes	●	●	●	●	●
Enlarged lymph nodes		●	✕	✕	✕
Enlarged spleen, liver, or both			●	✕	✕
Low numbers of red blood cells				●	✕
Low numbers of platelets					●

● required criterion ✕ may occur

Why start treatment?

It's important to talk with your oncologist about starting treatment. Share your wishes and concerns. Together, you can decide when it's time to start treatment.

In general, oncologists recommend starting treatment when the effects of cancer become worse than the risks of treatment. At this point, treatment may make you feel better.

A high white blood cell count by itself is not a reason to treat CLL. Reasons to start treatment are listed in **Guide 4.**

"I found focusing and staying in touch with a small circle of close friends who really care about you helped build my mental strength. It will be easy to identify them, and the good feeling you have after a text or chat is great mental strength fuel."

Guide 4 Reasons to start treatment
You can enroll in a clinical trial that assesses if early treatment is helpful.
You have major symptoms of CLL as described in Chapter 1: *About CLL*.
CLL is causing one or more of your organs to stop working properly.
Your spleen or lymph nodes have enlarged, are growing quickly, or are causing discomfort.
CLL is causing your red blood cell count to be low.
CLL is causing your platelet count to be low.
Your body doesn't respond to steroids like it should (steroid-refractory autoimmune cytopenia).

Key points

- CLL usually grows very slowly, so treatment may not be needed for months or years. Early treatment of CLL won't help you live longer.
- Your care team will regularly check the status of your CLL during watch and wait.
- During watch and wait, you can take care of your health by going to appointments, finding support, and living a healthy lifestyle.
- Higher cancer stages are more likely to need treatment sooner than lower stages.
- Treatment is started based on your wishes and advanced signs and symptoms of CLL.

Questions to ask

- What is my Rai stage? Does this stage mean my cancer is advanced?
- Do I have to start treatment right away?
- What can I do to be healthy if I don't need treatment right away?

4
Treatment for CLL

In the past few years, there have been new breakthroughs in treating chronic lymphocytic leukemia (CLL). Discuss the treatment options in this chapter with your family and your care team. Treatment will be designed specifically for you.

"I found tremendous comfort in focusing on the things that I could control, such as taking medications as directed, taking an active role in educating myself about my disease and my treatment plan, and ensuring I asked for (and received) proper care."

About treatment

A team of experts will provide your cancer treatment and support you. Your team will be led by a hematologist-oncologist—an expert in treating blood cancers. Other common team members include nurses, physician assistants, patient navigators, social workers, and specialists.

Chronic lymphocytic leukemia (CLL) is treated with cancer medicine, like pills, capsules, or intravenous medicines. Some treatments consist of one or more drugs. In this chapter, preferred treatments are noted.

NCCN has 3 categories of preference for treatments:

- **Preferred therapies** have the most evidence they work better and may be safer than other therapies.
- **Other recommended therapies** may not work quite as well as preferred therapies, but they can still help treat cancer.
- **Therapies used in certain cases** work best for people with specific cancer features or health circumstances.

People with CLL are often treated over their lifespans with a series of different treatments. The first treatment given is referred to as first-line therapy. Second-line therapy is the second treatment, and so on.

All treatments can cause unwanted health problems called side effects. Side effects vary from person to person. Ask your care team for a list of possible side effects of your treatments. Also, tell your care team about any new or worsening symptoms you have. There may be ways to help you feel better. Care for key side effects is explained in Chapter 6: Supportive care.

Will I need tests before treatment?

CLL may change during watch and wait, and after treatment starts. The cancer will be tested before each line of treatment.

Biomarker tests

CLL differs between people. Differences in how CLL behaves are caused by abnormal changes in cancer cells. Not everyone with CLL has the same abnormal changes. Importantly, many of these changes can be identified, so they're called biomarkers. Because biomarkers differ between people, a treatment that helps one person might not help you. That's why it's important to have biomarker tests and get a treatment plan specific to you.

NCCN experts recommend testing for the following biomarkers before treatment:

- **A 17p deletion** is a missing part of chromosome 17 that contains the *TP53* gene.
- ***TP53* mutation** is an abnormal change in the *TP53* gene. This test is done because the *TP53* gene may be mutated instead of missing (deleted). This is different from the 17p deletion test.
- ***IGHV* mutation** is an abnormal change in the *IGHV* region genes. This biomarker does not change over time. So testing is only needed once.
- **A complex karyotype** is 3 or more unrelated defects in chromosomes that occur in more than one cell.

Biopsy and imaging

NCCN experts recommend a bone marrow biopsy and computed tomography (CT) scan only if needed. Most people with CLL won't need these tests.

A blood biomarker test is needed to pinpoint which treatments will work best for you.

Which treatment will I get first?

For many people with CLL, the first treatment is targeted therapy. Targeted therapy works by stopping how CLL cells grow and survive.

- **BTK inhibitors** are oral medications that target a protein called Bruton's tyrosine kinase (BTK) inside of CLL B cells. BTK helps send a signal that tells the B cells to grow. BTK inhibitors block BTK, which stops the CLL cells from growing.
- **BCL-2 inhibitors** are oral medications that target a protein called BCL-2 inside of B cells. BCL-2 can prevent the cancer cells from dying. BCL-2 inhibitors allow the cancer cells to die.

Your oncologist will choose a treatment based on several factors. Biomarker testing is important. If you have more than one change in your DNA, it's called a complex karyotype. Having a complex karyotype may limit how well BTK inhibitors work. Your age, overall health, and other medications are also important factors.

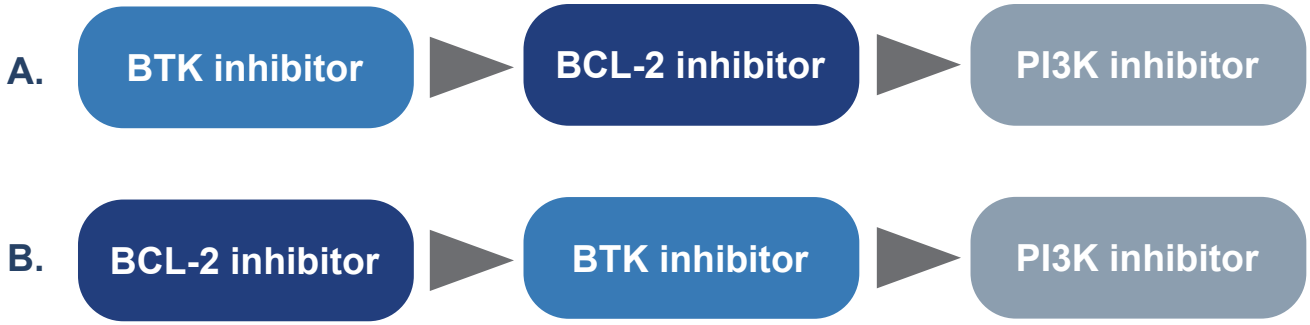
First-line therapy

First-line therapy is the first course of therapy you're given. The preferred first-line therapy you have may be a BTK inhibitor, a BCL-2 inhibitor, or perhaps a combination of both.

BTK inhibitors such as acalabrutinib (Calquence), zanubrutinib (Brukinsa), or ibrutinib (Imbruvica) are taken for as long as they are working. They are pills you take at home.

Treatment pathways

There are many treatment options for CLL, but some are more commonly used than others. Treatment for many people starts with either a BTK or BCL-2 inhibitor (shown below). In time, most people will need a different treatment. Often, treatment is switched from a BTK inhibitor to a BCL-2 inhibitor or the other way around. If you need a third type of treatment after taking BTK and BCL-2 inhibitors, there are also many options. One of these options is a PI3K inhibitor.



The only BCL-2 inhibitor available as of this writing is venetoclax (Venclexta). It's a pill you take at home. **See Guide 5** for a list of treatments for first-line therapy.

Before starting a BTK inhibitor, your oncologist may assess your risk for diseases that affect your heart or blood vessels, commonly called cardiovascular disease. BTK can cause cardiovascular problems in rare cases.

One BTK treatment option is acalabrutinib (Calquence). Obinutuzumab (Gazyva) is sometimes added to it. Zanubrutinib (Brukinsa) is used by itself to treat CLL.

Ibrutinib (Imbruvica) often has very good results but appears to cause more serious side effects, including heart disease, than other BTK inhibitors. A CD20 antibody may be used with ibrutinib, but more research is needed on these treatments.

Some people with CLL may prefer venetoclax over BTK inhibitors. At first, venetoclax is taken for 1 year and can reduce CLL to very low levels. Taking venetoclax for a fixed time

Guide 5
First-line treatments for CLL

	Treatment	CLL without 17p deletion and *TP53* mutation	CLL with 17p deletion or *TP53* mutation
BTK inhibitors	**Acalabrutinib with or without obinutuzumab**	Preferred	Preferred
	Zanubrutinib	Preferred	Preferred
	Ibrutinib	Other recommended regimen	Other recommended regimen
	Ibrutinib and obinutuzumab	Other recommended regimen	
	Ibrutinib and rituximab	Other recommended regimen	
BCL-2 inhibitors	**Venetoclax with obinutuzumab**	Preferred	Preferred
BTK and BCL-2 inhibitors	**Ibrutinib and venetoclax**	Other recommended regimen	Other recommended regimen

may prevent CLL from becoming unresponsive (resistant) to it.

Some research has been done on treatment with both ibrutinib and venetoclax. This treatment starts with taking only ibrutinib and then adding venetoclax. It's taken for a limited amount of time.

Second-line therapy and after

The next treatment is based on the results of prior treatments. **See Guide 6** for a list of treatments for second-line and after therapy.

If CLL grows, the type of treatment is often switched. You may switch to a BTK inhibitor after a BCL-2 inhibitor or the other way around. Another option combines ibrutinib (Imbruvica), a BTK inhibitor, and venetoclax (Venclexta), a BCL-2 inhibitor.

There is a third option if CLL grows after venetoclax (Venclexta) treatment is finished. This growth is called progression, and CLL may be treated with venetoclax again. Venetoclax may be taken with a CD20 antibody for a limited time.

Guide 6
Second-line treatments for CLL

	Treatment	CLL without 17p deletion and *TP53* mutation	CLL with 17p deletion or *TP53* mutation
BTK inhibitors	Acalabrutinib	Preferred	Preferred
	Zanubrutinib	Preferred	Preferred
	Ibrutinib	Other recommended regimen	Other recommended regimen
BCL-2 inhibitors	Venetoclax and rituximab	Other recommended regimen	Other recommended regimen
	Venetoclax	Other recommended regimen	Preferred
	Venetoclax and obinutuzumab	Preferred	Preferred
BTK and BCL-2 inhibitors	Ibrutinib and venetoclax	Other recommended regimen	Other recommended regimen

Obinutuzumab (Gazyva) is the preferred CD20 antibody. Venetoclax (Venclexta) may also be used by itself or combined with rituximab (Rituxan) for as long as it controls cancer growth.

If treatment causes severe side effects, the type of treatment is often switched. If you're taking a BTK inhibitor, the next option is to take a different BTK inhibitor. A different inhibitor—acalabrutinib (Calquence), zanubrutinib (Brukinsa), or ibrutinib (Imbruvica)—may have less severe effects.

In third-line treatment and any treatments that follow, pirtobrutinib (Jaypirca) is sometimes useful. It's a BTK inhibitor that works differently than other BTK inhibitors. It's an option after treatment with one or more of the other BTK inhibitors.

What's chemoimmunotherapy?

Most people start with targeted therapy, but sometimes it's useful to first treat CLL with chemoimmunotherapy or immunotherapy.

- **Chemotherapy** kills fast-growing cells like cancer.
- **Immunotherapy** enables your immune system to kill cancer.
- **Chemoimmunotherapy** combines chemotherapy and immunotherapy.

Chemoimmunotherapy and immunotherapy are given in cycles. One cycle is a period of treatment days followed by days of rest.

Almost all the drugs are given as a slow injection called an infusion.

Chemoimmunotherapy may also be started if targeted therapy is not possible.

Chemoimmunotherapy

Chemotherapy alone was once the standard treatment for CLL. Often, it didn't have great results. Experts now know that it doesn't work well for CLL with 17p deletion or *TP53* mutation. So chemotherapy is only an option for CLL without 17p deletion and *TP53* mutation.

First-line chemoimmunotherapy for CLL includes CD20 antibodies. CD20 antibodies are a type of immunotherapy. They include obinutuzumab (Gazyva) and rituximab (Rituxan).

The fludarabine, cyclophosphamide, and rituximab (FCR) treatment works well for CLL with *IGHV* mutations but can cause severe side effects. So FCR is only recommended for people who are under 65 years of age and fairly healthy.

Chemoimmunotherapy may be received when first-line targeted therapy isn't an option. It's also sometimes used if a rapid decrease in the amount of cancer is needed. In these cases, the options are bendamustine with either obinutuzumab or rituximab, or obinutuzumab with chlorambucil (Leukeran).

Immunotherapy alone

Immunotherapy (without chemotherapy) is sometimes used for first-line therapy for the same reasons as chemoimmunotherapy. But it's a treatment option for CLL with or without 17p deletion and *TP53* mutation.

One immunotherapy treatment option is obinutuzumab. Another treatment option is a combination of either CD20 antibody (obinutuzumab or rituximab) or high-dose methylprednisolone (HDMP).

What comes after BTK and BCL-2 inhibitors?

If you've tried all of the BTK and BCL-2 treatment options, you still have several options remaining:

- Clinical trials
- Hematopoietic cell transplant

Guide 7
Treatments after BTK and BCL-2 inhibitors

Treatment	CLL without 17p deletion and *TP53* mutation	CLL with 17p deletion or *TP53* mutation
Duvelisib	Preferred	Preferred
Zanubrutinib	Other recommended regimen	Other recommended regimen
Alemtuzumab with or without rituximab		Other recommended regimen
Bendamustine and rituximab	Other recommended regimen	
Fludarabine, cyclophosphamide, and rituximab (FCR)	Other recommended regimen	
High-dose methylprednisolone (HDMP) with either rituximab or obinutuzumab	Other recommended regimen	Other recommended regimen
Ibrutinib and venetoclax	Other recommended regimen	Other recommended regimen
Lenalidomide with or without rituximab	Other recommended regimen	Other recommended regimen
Obinutuzumab	Other recommended regimen	

- A recommended drug treatment, shown in **Guide 7**. Many of these drugs work differently than others you've had already.

Clinical trial

Experts are researching ways to better treat CLL in people who've already tried BTK and BCL-2 inhibitors. Ask your care team if there's a clinical trial that's a good fit for you. A clinical trial may provide access to a new way of stopping CLL that isn't available otherwise.

Because of clinical trials, new treatments, such as pirtobrutinib (Jaypirca), are now available to everyone. For more information on clinical trials, turn to the *Clinical trials* section in this chapter.

Hematopoietic cell transplant

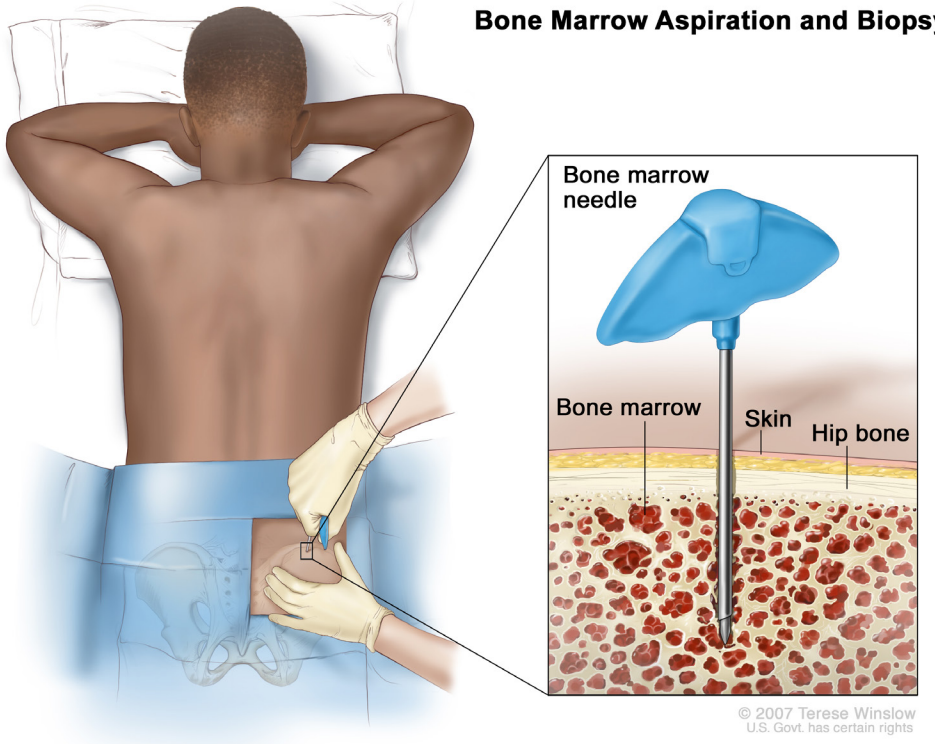
To have a hematopoietic cell transplant, you must not have major health problems other than cancer. Most people with CLL do not get a transplant.

A hematopoietic cell transplant uses donor cells to form healthy bone marrow. Blood-forming stem cells are collected from a close relative or a stranger using a bone marrow biopsy. These cells come from the bone marrow and can develop into any type of blood cell. This process is also known as allogeneic cell transplantation.

It may take some time to get the transplant. While you wait, you may get other treatments to reduce spleen size and improve symptoms.

Bone Marrow Aspiration and Biopsy

Doctors use a bone marrow biopsy and aspiration to remove samples of solid bone marrow and liquid bone marrow for testing. These samples are often removed at the same time on the pelvic bone.



Recommended drug treatments

After treatment with BTK and BCL-2 inhibitors, there are a few more treatments for CLL. Also, some treatments that were options earlier are options now, too. **See Guide 7** for a complete list.

- A PI3K inhibitor like duvelisib (Copiktra) is used by itself to treat CLL. Another PI3K inhibitor, idelalisib (Zydelig), may be taken with or without rituximab.
- Alemtuzumab (Campath) is a CD52 antibody—a type of immunotherapy—used to treat CLL. It marks the cancer cells so that the immune system can find and destroy the cells. Alemtuzumab may be received with or without the CD20 antibody rituximab (Rituxan). This drug is not used routinely for CLL.
- Lenalidomide (Revlimid) is an immunomodulatory drug for CLL. It affects the immune system in multiple ways. It's used by itself or with rituximab to treat CLL.
- Chemoimmunotherapy is an option only for CLL without 17p deletion and *TP53* mutation. Fludarabine, cyclophosphamide, and rituximab (FCR) is an option for people who are under 65 years of age and healthy. Another recommended chemoimmunotherapy option is bendamustine (Bendeka) with rituximab (Rituxan).
- Immunotherapy can also be used after BTK and BCL-2 inhibitors. One option is obinutuzumab (Gazyva). Another is high-dose methylprednisolone (HDMP) with either rituximab (Rituxan) or obinutuzumab.

How do I know if the treatment is working?

To learn about results, read *Checking treatment responses* on page 35. If CLL grows, the possible targeted therapies would be started next (see previous section, *What comes after BTK and BCL-2 inhibitors?*).

"The key to managing fear is in making informed decisions. Stay positive, make a plan for yourself, and go forward one step at a time."

Clinical trials

A clinical trial is a type of medical research study. After being developed and tested in a lab, potential new ways of fighting cancer need to be studied in people.

If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

Phases

Most cancer clinical trials focus on treatment and are done in phases.

- **Phase 1** trials study the safety and side effects of an investigational drug or treatment approach.
- **Phase 2** trials study how well the drug or approach works against a specific type of cancer.
- **Phase 3** trials test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase 4** trials study the safety and benefit of an FDA-approved treatment.

Who can enroll?

It depends on the clinical trial's rules, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. They ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

Finding a clinical trial

In the United States

NCCN Cancer Centers
NCCN.org/cancercenters

The National Cancer Institute (NCI)
cancer.gov/about-cancer/treatment/clinical-trials/search

Worldwide

The U.S. National Library of Medicine (NLM)
clinicaltrials.gov

Need help finding a clinical trial?

NCI's Cancer Information Service (CIS)
1.800.4.CANCER (1.800.422.6237)
cancer.gov/contact

Informed consent

Clinical trials are managed by a research team. This group of experts will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this

information is also provided in an informed consent form. This agreement confirms that you've been fully told about your part in the trial. Read the form carefully and ask questions before signing it. Take time to discuss it with people you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in cancer clinical trials. It is common to receive either a placebo with a standard treatment, or a new drug with a standard treatment. You will be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll.

Are clinical trials free?

There is no fee to enroll in a clinical trial. The study sponsor pays for research-related costs, including the study drug. But you may need to pay for other services, like transportation or childcare, due to extra appointments. During the trial, you will continue to receive standard cancer care. This care is often covered by insurance. If you are considering participation in a trial, speak with a clinic social worker or financial navigator to learn if financial or travel assistance is available.

Checking treatment responses

To find out how well your treatment is working, you'll need to have tests to assess the treatment response. These tests include an updated medical history, physical exam, blood tests, and sometimes imaging.

Types of responses

Based on tests, the response to treatment may be one of the following:

- Complete remission is the best result. With a complete remission, swollen organs and lymph nodes are back to normal size. You have no cancer symptoms, like fever. Blood counts are within normal range. No CLL cells are detected in the bone marrow with common tests.
- Partial remission is a good result. Swollen organs and nodes have shrunk to less than half their size. Blood counts have improved, but are not normal.
- Stable disease is less than a partial remission. CLL is not growing, but it hasn't gone away either.
- Progressive disease means CLL is still growing.

CLL not in remission

The next steps of treatment depend on the type of outcome. Your treatment plan may not change if CLL is stable. If CLL is growing, you'll likely start a different type of treatment. For some people, more tests are needed to plan treatment.

Testing for mutations

If you're on a BTK inhibitor, CLL may not be in remission because you may have *BTK* or *PLCG2* mutations. If tests find a mutation, you may switch treatment if the cancer is growing. If the cancer is stable, you can keep taking the same BTK inhibitor because it may control cancer growth for a couple of years.

Testing for transformed CLL

If CLL is growing while on any type of treatment, it may have transformed. CLL can change into a faster-growing cancer, which is described in *Chapter 5: Richter transformation*. This doesn't happen often. Transformed CLL is confirmed by lab tests on a biopsy sample.

CLL in remission

After remission is achieved, your care team will monitor the status of your CLL at regular follow-up visits. You may continue to receive treatment during remission.

At visits, your medical history will be updated. You'll have a physical exam and blood tests.

Testing for minimal residual disease

When CLL is in complete remission, your oncologist may want to test for minimal residual disease, or MRD. After successful treatment, there could still be a tiny amount of cancer cells in the blood even though no cancer cells can be seen with a microscope. This tiny amount of cancer is called minimal residual disease.

Very sensitive lab tests are used to detect minimal residual disease.

A finding of undetectable minimal residual disease means the test detected no CLL cells. There may be no CLL cells or too few to be found by the most sensitive test. Despite these great results, CLL may not be cured.

Relapse

CLL tends to worsen over time. But it may take years before you need a new treatment. The return of CLL after at least 6 months of remission is called a relapse.

If you receive a BTK inhibitor by itself, it is continued until there is a relapse or serious side effects. At that time, a different treatment may need to be started quickly.

At this point you may receive chemoimmunotherapy and immunotherapy for a limited time. For most people, venetoclax is also taken for a fixed amount of time.

If the amount of CLL is low and there are no symptoms or side effects as a result of your blood counts, then the BTK inhibitor may be continued if that is the current treatment, or you may be followed with watch and wait.

Swollen lymph nodes or a larger liver or spleen are signs of a relapse. So is a large increase in the number of white blood cells called lymphocytes.

At relapse, treatment is started when there are signs that it is needed. These signs are explained in *Chapter 4: Treatment for CLL.*

A chimeric antigen receptor (CAR) T-cell therapy, lisocabtagene maraleucel (Breyanzi), is recommended for relapsed CLL or if the CLL is resistant to other medications.

Key points

- Before starting treatment, you'll need to be tested for any biomarkers that could affect your options. New biomarkers may appear during watch and wait or after first-line therapy.
- A clinical trial tests new ways of stopping cancer in people. Ask your care team if there are clinical trials that are a good fit for you. A clinical trial may be an option at any time during treatment.
- The first treatment for chronic lymphocytic leukemia (CLL) is often either ~~a~~ Bruton's tyrosine kinase (BTK) or a BCL-2 inhibitor. These treatments control cancer growth well.
- If the cancer grows or there are severe side effects, the type of treatment is often switched. You may switch to a BTK inhibitor after having a BCL-2 inhibitor or the other way around.
- If BTK and BCL-2 inhibitors stop working, you may have the option of a hematopoietic cell transplant or a recommended drug treatment such as chimeric antigen receptor (CAR) T-cell therapy.

Questions to ask

- What are the possible complications and side effects of treatment?
- Are there any long-term or permanent side effects?
- Do any medications worsen side effects?
- Do you recommend that I consider a clinical trial for treatment?

5
Richter transformation

In some people, chronic lymphocytic leukemia (CLL) changes into an aggressive disease. This change is called Richter transformation or Richter syndrome. It can occur before or after treatment of CLL.

"I'm newly diagnosed and filled with anxiety. I'm glad I joined an educational webinar, it was very helpful."

In rare cases, chronic lymphocytic leukemia (CLL) can rapidly transform into a more serious cancer. Most often, it transforms into diffuse large B-cell lymphoma (DLBCL). Less often, it changes into Hodgkin lymphoma. In either case, this shift is called Richter transformation.

Richter transformation can evolve from mutations within CLL cells or from another B cell. Richter transformation has a poor outlook.

What tests are for Richter transformation?

Tests are needed to confirm Richter transformation and plan treatment. These tests are like those for CLL described in *Chapter 3: Watch and wait.*

Confirming transformed CLL

Rapidly growing lymph nodes or masses or high blood levels of lactate dehydrogenase (LDH) can point to Richter transformation. A biopsy, or sample, of lymph nodes is needed to confirm the diagnosis.

Imaging may be used to select the best area to sample. Options for imaging are a whole-body PET/CT scan or a diagnostic CT scan of the chest, abdomen, and pelvis.

A CT scan uses x-rays to generate a series of cross-sectional images of the inside of your body.

A PET/CT scan involves injecting a safe radioactive chemical into your body. The care team will then use a machine to see where the chemical stays the most, which can pinpoint places with lots of cancer cells.

An excisional biopsy is when a whole lymph node is removed by a surgeon, while an incisional biopsy would remove part of one.

A hematopathologist will examine and test the lymph node samples. They will look for signs of transformation, such as large and active lymphoma cells.

If results from the lymph node biopsy aren't clear, a bone marrow biopsy may be done next.

Planning treatment for Richter transformation

Your care team will ask about your current and past health to obtain your medical history. Your oncologist will examine your body and look for enlarged lymph nodes and organs.

You'll need to get blood drawn through a needle placed in your arm, so a complete blood count (CBC) with differential and comprehensive metabolic panel can be done.

Additional tests on blood samples can help plan supportive care. Tests of LDH can help assess for a condition called autoimmune hemolytic anemia. In this condition, your immune system mistakenly attacks your red blood cells, causing low blood levels.

Tests of uric acid levels can show if you've developed tumor lysis syndrome.

Old viruses in your body may reactivate, so testing for Epstein-Barr and hepatitis viruses is useful. Read *Chapter 6: Supportive care* for information on supportive care.

Depending on your treatment options, you might get a heart scan or a human leukocyte antigen (HLA) test. A scan of your heart is needed to decide if a drug called anthracycline is safe. An HLA test is needed to find a donor for a hematopoietic cell transplant.

Some cancer treatments can damage reproductive organs and harm unborn babies. You may receive a referral to a fertility specialist before starting cancer treatment.

If needed, your care team will also check if you're pregnant.

How is Richter transformation treated?

Treatment starts right after diagnosis. The goal of treatment is to extend life.

Treatment is based on the type of lymphoma CLL transformed into.

DLBCL

Diffuse large B-cell lymphoma (DLBCL) tumors consist of fast-growing, large B cells. They're commonly found in lymph nodes, spleen, liver, bone marrow, or other tissues and organs.

Symptoms can include fever, night sweats, fatigue, and weight loss. These symptoms are referred to as B symptoms. Not everyone has the same symptoms and tumors can be found anywhere in the body. The treatments that are recommended depend on whether DLBCL evolved from CLL cells.

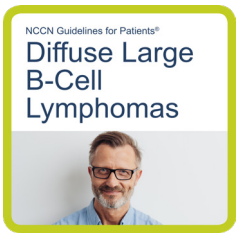
For DLBCL that evolved from CLL cells, a clinical trial is preferred. Ask your care team if there is an open trial that's a good fit for you. If a clinical trial is not an option, rituximab-based chemoimmunotherapy is often used for treatment, but BTK and immune checkpoint inhibitors are also options. **See Guide 8.** Also, new treatments may be available through clinical trials.

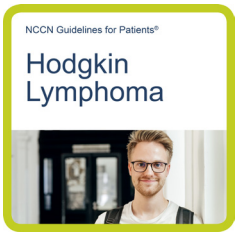
If DLBCL did not evolve from CLL cells, the standard treatment recommendations for DLBCL are followed. These recommendations for treating DLBCL are available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Hodgkin lymphoma

In Hodgkin lymphoma, lymphocytes appear abnormally large and may have more than one nucleus. A nucleus is the control center of the cell.

A clinical trial is the preferred treatment for Richter transformation to Hodgkin lymphoma. The other recommended option is chemotherapy treatments. Treatment information for Hodgkin lymphoma is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.





Guide 8
Treatments for Richter transformation from CLL cells to DLBCL

Chemoimmunotherapy	DA-EPOCH-R: Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab
	R-HyperCVAD: Rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine
	OFAR: Oxaliplatin, fludarabine, cytarabine, and rituximab
	RCHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
	Venetoclax with RCHOP
BTK inhibitors	Pirtobrutinib
	Acalabrutinib
	Zanubrutinib with tislelizumab-jsgr
Immune checkpoint inhibitors	Nivolumab with or without ibrutinib
	Pembrolizumab with or without ibrutinib

Key points

- Richter transformation is a change from CLL to an aggressive lymphoma. The diagnosis is confirmed with a biopsy of lymph nodes or bone marrow.
- Richter transformation to DLBCL is typically treated with rituximab-based chemoimmunotherapy if a clinical trial isn't an option.
- Richter transformation to Hodgkin lymphoma typically is treated with chemotherapy if a clinical trial isn't available.

Questions to ask

- What is the treatment that would be appropriate for me now that I have Richter transformation?
- What are the symptoms of Richter transformation?
- Do you follow NCCN recommendations to treat DLBCL and Hodgkin lymphoma?

6
Supportive care

The goal of supportive care is to maintain or improve your quality of life. It's used to prevent or relieve health problems caused by chronic lymphocytic leukemia (CLL) or its treatment.

Who is supportive care for?

Supportive care is a key part of treatment for everyone with chronic lymphocytic leukemia (CLL).

Supportive care helps improve your quality of life during and after cancer treatment. The goal is to prevent or manage side effects and symptoms, like pain and cancer-related fatigue. It also addresses the mental, social, and spiritual concerns faced by those with cancer.

Supportive care is available to everyone with cancer and their families, not just those at the end of life. Palliative care is another name for supportive care.

Supportive care can also help with:

- Making treatment decisions
- Coordinating your care
- Paying for care and transportation assistance
- Planning for advanced care and end of life

Get the vaccines recommended by your oncologist. They will help protect you against infections.

This chapter describes some of the unique needs of people with CLL. People with CLL are more likely than other people to get infections, develop second cancers, and have other health problems. This chapter also lists NCCN resources on supportive care.

What vaccines should I get?

You can protect yourself by being up to date on your vaccines. Vaccines help prevent infections by training your body to quickly recognize and attack germs. They contain whole germs, parts of a germ, or a product of a germ, so your body can defend itself against future exposure.

Avoid live vaccines

You should avoid getting live vaccines unless approved by your oncologist. Live vaccines contain an entire germ that has been weakened (attenuated). They create a strong immune response to the real germ. Live vaccines may cause major health problems in people with weaker immune systems.

Get recommended vaccines

Vaccines are proven to be safe and effective in preventing serious illness. Some vaccines are routine. Others are based on age, health, and other factors. Talk to your care team about which vaccines you need.

NCCN experts recommend these vaccines for people with CLL:

- The flu shot (influenza vaccine) every year, but only a non-live type (inactive or recombinant)
- Pneumococcal vaccine, as recommended by the U.S. Centers for Disease Control and Prevention (CDC)
- Non-live (recombinant, adjuvanted) zoster vaccine to prevent shingles, if you're taking a BTK inhibitor
- COVID-19 vaccine (any type is acceptable)
- RSV for people over 65 years of age

COVID-19

More research is needed to learn how well the COVID-19 vaccine works among people with CLL. The vaccine may not fully protect you, but there are additional ways to protect yourself.

If there are a lot of COVID-19 cases in your area, protect yourself. Wear a mask. Keep a safe distance from others. Thoroughly wash your hands often.

If you do get COVID-19, there are treatments for it. Some COVID-19 treatments, like nirmatrelvir/ritonavir (Paxlovid), can interact with BTK inhibitors and venetoclax. While being treated for COVID-19, your oncologist might pause your cancer treatment.

CLL-related infections

Normally, there are germs in the body that are harmless. But when cancer treatments weaken the body's immune system, these germs can cause serious infections. Weakened immunity can also cause routine infections to be more severe. These unusual and severe infections are called opportunistic infections.

Preventing infections

Medicine used to treat infections can also be used for prevention. Preventive care is based on the type of treatment for CLL. Some cancer treatments weaken the immune system more than others.

Herpes and fungal pneumonia

Acyclovir (Zovirax) is an antiviral drug used to prevent infections caused by herpes viruses. These viruses include the herpes simplex virus and the varicella-zoster virus. The varicella-zoster virus causes chickenpox, and when reactivated in older people, shingles.

Trimethoprim-sulfamethoxazole (Sulfatrim, Bactrim) is a combined drug used to prevent pneumocystis jirovecii pneumonia. Pneumocystis jirovecii pneumonia is a lung infection caused by a common fungus.

Preventive care for herpes and fungal pneumonia is recommended during and after treatment with PI3K inhibitors, chemoimmunotherapy with fludarabine or bendamustine, and alemtuzumab. If you're taking a BTK inhibitor, your oncologist will provide preventive care and monitor for infection.

Neutropenia-related infections

While taking venetoclax (Venclexta), levels of white blood cells called neutrophils can drop. When levels of neutrophils are low, you're more likely to get infections. You'll need regular

You're not alone. Ask your care team about support groups in your area.

blood tests during treatment. The antibiotic fluoroquinolone and antifungal medicines help prevent infections caused by venetoclax-induced neutropenia.

Hepatitis

If you've had hepatitis B, it may come back during cancer treatment. Entecavir (Baraclude) is the preferred medicine to prevent and treat hepatitis B. Other options are adefovir, telbivudine (Tyzeka), and tenofovir (Viread). Preventive care may continue for up to 12 months after cancer treatment ends.

There's a link between hepatitis C and B-cell non-Hodgkin lymphomas. Direct-acting antiviral agents such as sofosbuvir (Sovaldi) safely treat hepatitis C and may reduce lymphoma cells.

Cytomegalovirus

If you've had cytomegalovirus, there's a high risk of cytomegalovirus reactivation when taking a PI3K inhibitor or alemtuzumab (Campath). Screening for reactivation should be done at least every 4 weeks. Reactivation may be prevented with the antiviral ganciclovir (Zirgan).

Treating ear, sinus, and lung infections

Some people with CLL get frequent, serious infections in their ears, sinuses, and lungs. Your oncologist will prescribe an antimicrobial, such as an antibiotic.

If your body isn't making enough immunoglobulin, you may receive purified, donated immunoglobulin in addition to an antimicrobial. Intravenous immunoglobulin (IVIG) is received every month through a needle placed in your arm, or you can get injections under the skin every week.

Could I get a second cancer?

People with CLL are at higher risk of getting other cancers, so regular cancer screening is important. There are screening programs for prostate, breast, cervical, lung, and colorectal cancers.

People with CLL are also at higher risk for melanoma and other skin cancers. Your risk is further increased if you sunburn easily or had major sun exposure as a child. See a dermatologist once a year for a skin exam.

What's autoimmune cytopenia?

Autoimmune cytopenia is a condition in which your immune system attacks your blood cells. There are several types. The most common types among people with CLL are autoimmune hemolytic anemia, immune-mediated thrombocytopenia, and pure red cell aplasia.

There are multiple treatment options for autoimmune cytopenia. Drug treatments include corticosteroids, rituximab, IVIG, cyclosporin A, eltrombopag, and romiplostim. If steroids don't work or the cytopenia returns, BTK inhibitors may be used for treatment.

For some cytopenias, surgery may be an option. The spleen plays a key role in destroying platelets. Removing the spleen, called a splenectomy, can help restore the number of platelets.

What's tumor lysis syndrome?

Several treatments for CLL kill many cells quickly, such as:

- Chemoimmunotherapy
- Venetoclax
- Lenalidomide
- Obinutuzumab

Tumor lysis syndrome occurs when the waste released by dead cells is not quickly cleared out of the body. This may result in kidney damage and severe blood electrolyte disturbances. It can be life-threatening.

Tumor lysis syndrome may be prevented with hydration. Drink lots of water. You may also get fluid infused into your bloodstream via a needle placed into a vein in your arm..

Medicines that lower uric acid can help, too. These medicines include allopurinol (Aloprim, Zyloprim), febuxostat (Uloric), or rasburicase (Elitek). Some people are admitted to the hospital before starting treatment.

What's tumor flare?

Lenalidomide may also cause tumor flare. Tumor flare is a fast, short-lived increase in cancer growth. Symptoms of tumor flare include enlarged lymph nodes or spleen, low-grade fever, and rash.

Steroids can prevent and treat tumor flare. Preventive care is typically started if lymph nodes are big. The skin rash and itchiness caused by the flare can be treated with antihistamines.

How should blood clots be treated?

Lenalidomide may cause blood clots.

A blood clot is a clump of blood that may block blood vessels. Clots can be dangerous. If you're not taking an anticoagulant, clots can be prevented with aspirin while on lenalidomide.

Aspirin is not needed if you are taking an anticoagulant like warfarin (Coumadin).

If not taking lenalidomide, your chance for blood clots may still be high. More information on blood clots and cancer is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

What if I'm bleeding or bruising?

BTK inhibitors increase the risk of bleeding and bruising. Your oncologist will monitor your bleeding risk based on all factors. Regular blood tests are very important since bleeding risk increases when platelets are low.

When taking a BTK inhibitor, NCCN experts recommend taking only 1 or 2 medicines that increase bleeding risk at the same time. It may be okay to take a BTK inhibitor and either aspirin or an anticoagulant. But taking a BTK inhibitor, antiplatelet, and an anticoagulant at the same time is risky.

If you need surgery, your oncologist may pause the BTK inhibitor to prevent major bleeding. The inhibitor is put on hold for 3 days before and after minor surgery. For major

surgery, treatment is paused for 7 days before and after surgery.

Will I need blood transfusions?

Some people being treated for CLL need a blood transfusion. The transfusion should be done according to hospital standards. All blood should be treated with radiation before the transfusion. This will prevent the rare event of transfused blood attacking your body.

Where can I go to learn more about supportive care?

The full library of NCCN Guidelines for Patients has several books on supportive care. These books focus on the treatment of common physical and emotional effects of many cancers.

The library of NCCN Guidelines for Patients is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Distress

Everyone with cancer feels distress at some point. It's normal to feel worried, sad, helpless, or angry. Distress can become severe and affect the way you live.

The full library of NCCN Guidelines for Patients has several books on supportive care at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Fatigue

Cancer-related fatigue is not the typical tiredness that follows an active or long day. It's a lack of energy that is distressing, does not improve with normal rest or sleep, and disrupts life.

Palliative care

Palliative care is an approach to health care for people living with serious illnesses, including cancer. It focuses on providing relief from the symptoms and stress of having cancer.

Nausea and vomiting

Both chemotherapy and radiation therapy can cause nausea and vomiting. Nausea is the feeling that you are going to throw up. Vomiting is forcefully throwing up what's in your stomach. Treatments are available to help with both complications.

Anemia and neutropenia

Chemotherapy often causes a drop in red and white blood cells. You're more likely to get infections when white blood cell counts are low. This is called neutropenia. A low number of red blood cells, called anemia, may cause fatigue.

Graft-versus-host disease

A possible side effect of hematopoietic cell transplant is graft-versus-host disease. This side effect is caused by the donor cells attacking your healthy cells.

Immunotherapy side effects

Immune checkpoint inhibitors are used to treat some types of Richter transformation. This treatment may cause your immune cells to attack your healthy cells. Immune-related side effects can occur during or after treatment.

CAR T-cell therapy side effects

Chimeric antigen receptor (CAR) T-cell therapy can cause serious side effects, including nervous system dysfunction. If you're having CAR T-cell treatment, review the *NCCN Guidelines for Patients: Immunotherapy Side Effects: CAR T-Cell Therapy.*

Late and long-term effects

Cancer and its treatment can cause long-term and late effects. Long-term effects start during treatment and persist after treatment is done. Less often, effects start long after treatment has ended. Late and long-term effects include fatigue, poor sleep, pain, and depression.

Healthy living

People with cancer need to start or maintain a healthy lifestyle. Healthy living may help prevent disease and improve well-being. Topics covered in this book include physical activity, food, tobacco use, and sun protection.

Key points

- Supportive care is cancer care that improves quality of life. It helps prevent life-threatening health conditions and provides symptom relief.
- People with chronic lymphocytic leukemia (CLL) are at risk for infections. Protect yourself by getting vaccinations but avoid attenuated vaccines because they contain live germs.
- Certain treatments for CLL can weaken the immune system. You may take medicines to prevent infections caused by weakened immunity. If you get frequent, severe infections, immunoglobulin may be added to your treatment.
- People with CLL are at risk for second cancers. Don't skip cancer screenings, as they can help detect new cancers early.
- Advanced CLL and some CLL treatments may cause your immune system to attack your blood cells. This is called autoimmune cytopenia. There are multiple treatment options including steroids.
- Several treatments for CLL may cause tumor lysis syndrome. Drinking water and staying hydrated help prevent this syndrome by removing dead cells from the body. Uric acid reducers may help, too.
- A tumor flare is a rapid increase in cancer growth right after starting lenalidomide. It's treated with steroids. Lenalidomide may also cause blood clots. Aspirin or an anticoagulant like warfarin (Coumadin) help prevent clots.

Questions to ask

- Who can I talk to about help with housing, food, transportation, and other basic needs?
- How can I connect with others and build a support system?
- How much will I have to pay for my treatment? What help is available to pay for medicines and other treatment?

7
Other resources

Want to learn more? Here's how you can get additional help.

What else to know

This book can help you improve your cancer care. It plainly explains expert recommendations and suggests questions to ask your care team. But it's not the only resource that you have.

You're welcome to receive as much information and help as you need. Many people are interested in learning more about:

- The details of their health and treatment
- Being a part of a care team
- Getting financial help
- Finding a care provider who is an expert in their field
- Coping with health problems

What else to do

Your health care center can help you with next steps. They often have on-site resources to help meet your needs and find answers to your questions. Health care centers can also inform you of resources in your community.

In addition to help from your providers, the resources listed in the next section provide support for many people like yourself. Look through the list and visit the provided websites to learn more about these organizations.

Where to get help

AnCan Foundation
Ancan.org

Bag It
bagitcancer.org

Blood & Marrow Transplant Information Network (BMT InfoNet)
BMTInfoNet.org

Cancer*Care*
Cancercare.org

Cancer Hope Network
cancerhopenetwork.org

CLL Society
cllsociety.org

Imerman Angels
Imermanangels.org

Leukemia Research Foundation
Leukemiarf.org

Lymphoma Research Foundation
lymphoma.org

National Bone Marrow Transplant Link (nbmtLINK)
nbmtlink.org

National Coalition for Cancer Survivorship
canceradvocacy.org

NMDP
nmdp.org/one-on-one

The Leukemia & Lymphoma Society (LLS)
LLS.org/PatientSupport

Triage Cancer
Triagecancer.org

Questions to ask

- Who can I talk to about help with housing, food, and other basic needs?
- What help is available for transportation, childcare, and home care?
- Are there other services available to me and my caregivers?
- How can I connect with others and build a support system?
- Who can I talk to if I don't feel safe at home, at work, or in my neighborhood?

Let us know what you think!

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.

NCCN.org/patients/response

Words to know

anemia
A health condition in which a blood protein called hemoglobin is low.

antibody
A protein in blood that helps fight off infection. Also called an immunoglobulin.

autoimmune hemolytic anemia
An attack on red blood cells by the disease-fighting (immune) system.

B cell
A type of white blood cell called a lymphocyte. Also called a B lymphocyte.

beta-2 microglobulin
A small protein made by many types of cells.

biopsy
A procedure that removes fluid or tissue samples to be tested for disease.

bone marrow
The sponge-like tissue in the center of most bones.

bone marrow aspiration
A procedure that removes a liquid bone marrow sample to test for a disease.

bone marrow biopsy
A procedure that removes bone and solid bone marrow samples to test for a disease.

B symptoms
A set of symptoms caused by some B-cell cancers.

cancer stage
A rating of the outlook of a cancer based on its growth and spread.

chemotherapy
Cancer drugs that stop the cell life cycle so cells don't increase in number.

chromosome
The structures within cells that package DNA and coded instructions for cell behavior (genes).

clinical trial
A type of research that assesses how well health tests or treatments work in people.

complete blood count (CBC)
A lab test that measures the number of red blood cells, white blood cells, and platelets.

comprehensive metabolic panel
Lab tests of up to 14 chemicals in your blood. Also called comprehensive chemistry panel.

computed tomography (CT)
A test that uses x-rays from many angles to make a series of pictures of the insides of the body.

contrast
A dye put into your body to make clearer pictures during imaging tests.

diagnosis
An identification of an illness based on tests.

differential
A lab test of the number of white blood cells for each type.

fatigue
Severe tiredness despite getting enough sleep that limits one's ability to function.

fertility counselor
An expert who helps people to have babies.

flow cytometry
A lab test of substances on the surface of cells to identify the type of cells present.

fluorescence in situ hybridization (FISH)
A lab test that uses special dyes to look for abnormal chromosomes and genes.

gene
Coded instructions in cells for making new cells and controlling how cells behave.

hematopathologist
An expert in diagnosing diseases of the blood.

hematopoietic cell transplant
A cancer treatment that replaces abnormal blood stem cells with healthy donor cells.

imaging
A test that makes pictures (images) of the insides of the body.

immune system
The body's natural defense against infection and disease.

immunoglobulin
A protein made by B cells to help fight off infection. Also called antibody.

immunomodulator
A cancer drug that modifies some parts of the body's disease-fighting system.

karyotype
A lab test that makes a map of chromosomes to find defects.

lactate dehydrogenase (LDH)
A protein in blood that helps to make energy in cells.

lymph
A clear fluid containing white blood cells.

lymph node
A small, bean-shaped, disease-fighting structure. Also called lymph gland.

lymph vessel
A small tube-shaped structure through which a fluid called lymph travels.

lymphatic system
A network of organs and vessels that collects and transports a fluid called lymph.

lymphocyte
One of three main types of white blood cells that help protect the body from illness.

lymphoma
A cancer of white blood cells called lymphocytes that are within the lymph system.

medical history
A report of all your health events and medications.

observation
A period of testing for changes in cancer status that signal treatment is needed.

performance status
A rating of one's ability to do daily activities.

physical exam
A study of the body for signs of disease.

positron emission tomography (PET)
A test that uses radioactive material to see the shape and function of body parts.

prognosis
The likely course and outcome of a disease.

pure red cell aplasia
A health condition in which the number of young red blood cells is very low.

Rai staging system
A rating scale of the outlook of chronic lymphocytic leukemia.

reticulocyte
A young red blood cell that is formed in bone marrow and is present briefly in blood.

Richter transformation
A change from a slow-growing leukemia into a fast-growing lymphoma. Also called Richter's syndrome.

side effect
An unhealthy or unpleasant physical or mental response to treatment.

spleen
An organ to the left of the stomach that helps protect the body from disease.

supportive care
Health care that includes symptom relief but not cancer treatment. Also called palliative care.

tumor lysis syndrome
A health condition caused by the rapid death of many cancer cells.

uric acid
A chemical that is made when cells and certain eaten food break down.

vaccine
A biological agent that is inserted into the body to prevent a disease.

We want your feedback!

Our goal is to provide helpful and easy-to-understand information on cancer.

Take our survey to let us know what we got right and what we could do better.

NCCN.org/patients/feedback

NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2025. It was adapted, reviewed, and published with help from the following people:

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NCCN Cancer Centers

Abramson Cancer Center
at the University of Pennsylvania
Philadelphia, Pennsylvania
800.789.7366 • pennmedicine.org/cancer

Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio
UH Seidman Cancer Center
800.641.2422 • uhhospitals.org/services/cancer-services
CC Taussig Cancer Institute
866.223.8100 • my.clevelandclinic.org/departments/cancer
Case CCC
216.844.8797 • case.edu/cancer

City of Hope National Medical Center
Duarte, California
800.826.4673 • cityofhope.org

Dana-Farber/Brigham and Women's Cancer Center |
Mass General Cancer Center
Boston, Massachusetts
877.442.3324 • youhaveus.org
617.726.5130 • massgeneral.org/cancer-center

Duke Cancer Institute
Durham, North Carolina
888.275.3853 • dukecancerinstitute.org

Fox Chase Cancer Center
Philadelphia, Pennsylvania
888.369.2427 • foxchase.org

Fred & Pamela Buffett Cancer Center
Omaha, Nebraska
402.559.5600 • unmc.edu/cancercenter

Fred Hutchinson Cancer Center
Seattle, Washington
206.667.5000 • fredhutch.org

Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah
800.824.2073 • healthcare.utah.edu/huntsmancancerinstitute

Indiana University Melvin and Bren Simon
Comprehensive Cancer Center
Indianapolis, Indiana
888.600.4822 • www.cancer.iu.edu

Johns Hopkins Kimmel Cancer Center
Baltimore, Maryland
410.955.8964
www.hopkinskimmelcancercenter.org

Mayo Clinic Comprehensive Cancer Center
Phoenix/Scottsdale, Arizona
Jacksonville, Florida
Rochester, Minnesota
480.301.8000 • Arizona
904.953.0853 • Florida
507.538.3270 • Minnesota
mayoclinic.org/cancercenter

Memorial Sloan Kettering Cancer Center
New York, New York
800.525.2225 • mskcc.org

Moffitt Cancer Center
Tampa, Florida
888.663.3488 • moffitt.org

O'Neal Comprehensive Cancer Center at UAB
Birmingham, Alabama
800.822.0933 • uab.edu/onealcancercenter

Robert H. Lurie Comprehensive Cancer Center
of Northwestern University
Chicago, Illinois
866.587.4322 • cancer.northwestern.edu

Roswell Park Comprehensive Cancer Center
Buffalo, New York
877.275.7724 • roswellpark.org

Siteman Cancer Center at Barnes-Jewish Hospital
and Washington University School of Medicine
St. Louis, Missouri
800.600.3606 • siteman.wustl.edu

St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center
Memphis, Tennessee
866.278.5833 • stjude.org
901.448.5500 • uthsc.edu

Stanford Cancer Institute
Stanford, California
877.668.7535 • cancer.stanford.edu

The Ohio State University Comprehensive Cancer Center -
James Cancer Hospital and Solove Research Institute
Columbus, Ohio
800.293.5066 • cancer.osu.edu

The UChicago Medicine Comprehensive Cancer Center
Chicago, Illinois
773.702.1000 • uchicagomedicine.org/cancer

The University of Texas MD Anderson Cancer Center
Houston, Texas
844.269.5922 • mdanderson.org

UC Davis Comprehensive Cancer Center
Sacramento, California
916.734.5959 • 800.770.9261
health.ucdavis.edu/cancer

UC San Diego Moores Cancer Center
La Jolla, California
858.822.6100 • cancer.ucsd.edu

UCLA Jonsson Comprehensive Cancer Center
Los Angeles, California
310.825.5268 • uclahealth.org/cancer

UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California
800.689.8273 • cancer.ucsf.edu

University of Colorado Cancer Center
Aurora, Colorado
720.848.0300 • coloradocancercenter.org

University of Michigan Rogel Cancer Center
Ann Arbor, Michigan
800.865.1125 • rogelcancercenter.org

University of Wisconsin Carbone Cancer Center
Madison, Wisconsin
608.265.1700 • uwhealth.org/cancer

UT Southwestern Simmons Comprehensive Cancer Center
Dallas, Texas
214.648.3111 • utsouthwestern.edu/simmons

Vanderbilt-Ingram Cancer Center
Nashville, Tennessee
877.936.8422 • vicc.org

Yale Cancer Center/Smilow Cancer Hospital
New Haven, Connecticut
855.4.SMILOW • yalecancercenter.org

Take our survey and help make the NCCN Guidelines for Patients better for everyone!

NCCN.org/patients/comments

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