LYMPHOMA RESEARCH • FOUNDATION

Understanding

Lymphoma and Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL/SLL)

Part 1 — Learning the Basics in Lymphoma

2023

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Chapter 1: Understanding the Disease

Lymphoma is a type of blood cancer that can affect white blood cells called *lymphocytes*, in the *lymphatic system* (tissues and organs that produce, store and carry white blood cells), the blood, and the *bone marrow* (the spongy tissue inside large bones such as the pelvis, vertebrae and ribs). Normally, lymphocytes work together with other cells of the immune system to defend the body against bacteria, viruses, parasites, and other foreign substances. They can also fight cancer cells. Lymphocytes travel in the bloodstream and in the lymphatic system to accumulate in specialized structures called lymph nodes (bean-shaped structures that help the body fight infection), in the bone marrow, and in the spleen. Lymph nodes are part of the lymphatic system and typically are the sites in which the body develops an immune response (the immune system recognizes and attacks harmful or foreign substances) to viruses and bacterial infections.

This chapter explains these and other terms that will help people understand lymphoma and how it affects a person's health so patients can better participate in their care.

What is Cancer?

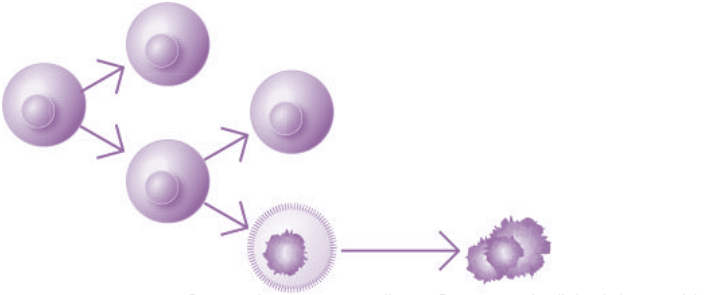
The body is made up of many different types of specialized cells organized into tissues and organs, which perform the tasks needed to sustain life. To keep the body running smoothly, cells in the body grow, work, and multiply in a very controlled fashion.

Most normal cells have a limited lifespan after which a self-destruct mechanism (process) is triggered for cells that are *senescent* (too old) or get damaged; this process is called *apoptosis* or programmed cell death. However, sometimes *mutations* (permanent changes) in the genetic material (DNA) of a cell overcome this self-destruct mechanism and allow the cell to continue to live and grow indefinitely, preventing the damaged cell from ever dying. Usually, the body's immune system identifies and gets rid of these cancerous cells, but sometimes these can escape the immune

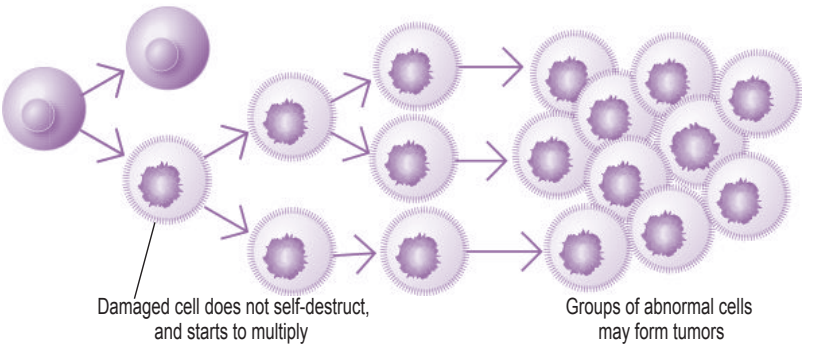
system, multiply uncontrollably, and pile up forming a mass called a tumor that can grow to interfere with normal organ function.

HOW CANCER FORMS INSIDE THE BODY

Normal cell division



Cancer cell division



Most cancers are named after the organ or cell where the cancer originated. For example:

- A cancer that started in the pancreas is called pancreatic cancer.
- A cancer of the lymphocytes is called a *lymphoma* or *lymphocytic leukemia* depending on whether the cancerous lymphocytes are located primarily in the lymph nodes and other lymphatic tissues (lymphoma) or primarily in the bone marrow and the blood (lymphocytic leukemia).

What Are the Different Types of Blood Cells?

There are three main classes of blood cells:

- Red blood cells (or *erythrocytes*) — Red blood cells carry oxygen from the lungs to all the tissues in the body. Red blood cells also remove the carbon dioxide waste produced by cells and bring it to the lungs to be exhaled. A low number of red blood cells is called *anemia*. A person with anemia may feel tired, weak, and short of breath.
- Platelets (or *thrombocytes*) — Platelets are cell fragments produced by cells in the bone marrow. They clump together in a blood clot to stop bleeding from broken blood vessels. A low number of platelets is called *thrombocytopenia*. People with thrombocytopenia are more likely to bruise and bleed with minor trauma. They are also more likely to have severe and recurring nosebleeds and bleeding gums.
- White blood cells (or *leukocytes*) — White blood cells work as part of the immune system to help the body fight infections. The main types of white blood cells are:
  - *Granulocytes* — There are three types of granulocytes: neutrophils, basophils, and eosinophils. Neutrophils help fight bacterial infections. A low number of neutrophils in the blood is called *neutropenia*. People with neutropenia are more likely to get infections (mostly bacterial infections). Basophils are cells that take part in inflammatory reactions (i.e., an immune response against injury or infection that can cause symptoms such as fever, redness, swelling, and pain). Eosinophils also help fight infections, particularly those caused by parasites, and they become plentiful during allergic reactions.
  - *Monocytes* — These also play an important role in immunity by attacking cells infected with viruses or bacteria. They also get rid of senescent (too old) cells.
  - Lymphocytes — These are discussed below.

Blood cells have a varied lifespan from a few hours (e.g., neutrophils) to more than 3 months (e.g., red blood cells). Therefore, the body needs to constantly maintain its supply of these cells. New blood cells are made by *hematopoietic* (blood-forming) *stem cells* found in the bone marrow, which are immature (nonspecialized) cells that can develop into any kind of blood cell as needed.

What Are Lymphocytes?

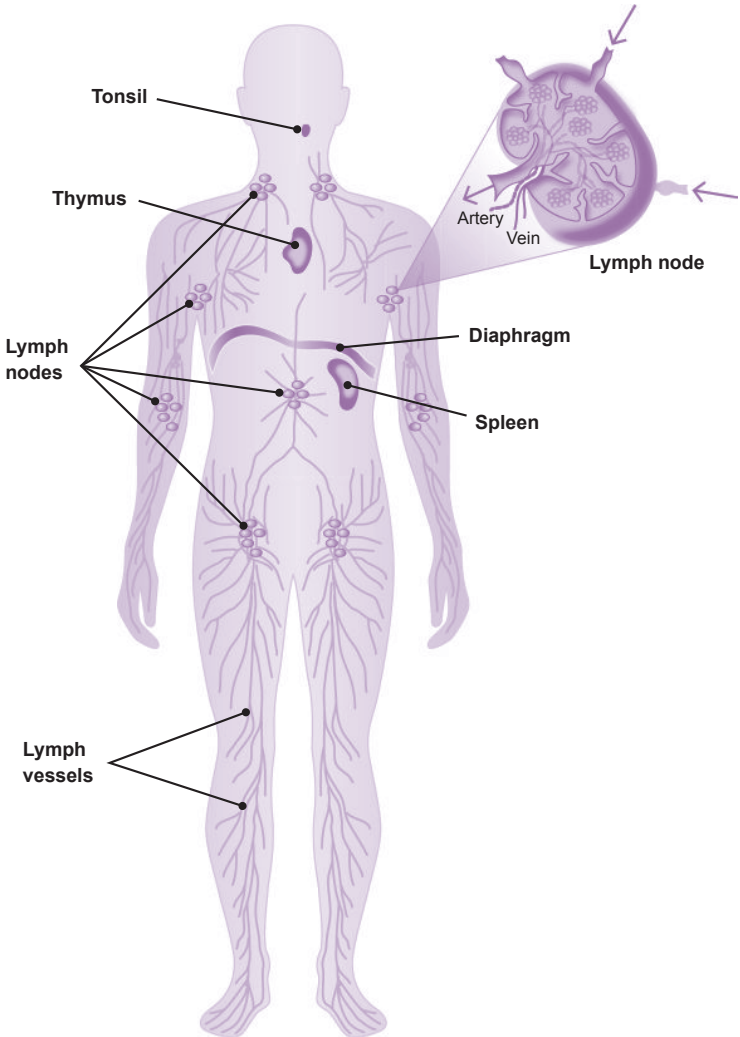
Lymphocytes are a type of white blood cell. There are three main types of lymphocytes:

- B lymphocytes (B-cells) — B-cells make antibodies to fight infections. They are called "B" cells because they were first discovered in the "Bursa of Fabricius" in birds (similar to the appendix in humans). Later, similar cells were found in humans.
- T lymphocytes (T-cells) — These cells can be considered the "coordinators" of the immune system. Some help B-cells make antibodies, some attack and kill infected cells, and others help control or regulate the way other parts of the immune system fight infections. They are called "T" cells because they develop in the thymus gland, a small organ in the front of the chest.
- Natural killer (NK) cells — NK cells attack and kill cancer cells and virus-infected cells. They also make proteins called cytokines that help the body get rid of viruses and tumor cells.

What is the Lymphatic System?

As shown in the following image, the lymphatic system is a spidery network of thin tubes called lymphatic vessels, somewhat similar to the blood vessels that make up the circulatory system (the system that moves blood across the body). Like blood vessels, lymphatic vessels branch out into all tissues of the body. Lymphatic vessels carry *lymph*, a liquid that contains lymphocytes to help fight infection. Thanks to the lymphatic and circulatory system, immune cells are free to move around and reach areas of the body where an infection or an injury occurred.

THE LYMPHATIC SYSTEM



Within this huge network of vessels are groups of lymph nodes, which are also commonly known as “glands.” Lymph nodes filter the lymph fluid, removing bacteria, viruses, and other foreign substances from the body. Hundreds of lymph nodes are normally found at locations throughout the body, including the neck, underarms, chest, abdomen, and groin.

Lymphocytes can mostly be found in lymph nodes, where they monitor the body's immune system for signs of infection. The lymph nodes can change in size, becoming bigger or smaller depending on the number of lymphocytes inside them.

If large numbers of foreign substances are filtered through a lymph node or series of lymph nodes, swelling may occur, and the nodes may become tender to the touch. Most swollen lymph nodes are a reaction to infection and are not cancerous. Lymph nodes can also become enlarged in states of inflammation, such as in autoimmune diseases (the body's immune system mistakes its own healthy cells for abnormal cells and attacks them) like rheumatoid arthritis.

How Does the Immune System Work?

The immune system is the body's defense against things that might cause it harm. The immune system is made up of a network of cells, tissues, and organs that work together to detect and destroy invaders, such as bacteria, viruses, and parasites, that can make people sick.

The immune system provides two different types of immunity:

- *Innate* (meaning "inborn" or "natural") immunity — This type of immunity is provided by natural barriers in the body, substances in the blood, and specific cells that attack and kill foreign cells. Examples of natural barriers include skin, mucous membranes, stomach acid, and the cough reflex. These barriers keep germs and other harmful substances from entering the body. *Inflammation* (redness and swelling) is also a type of innate immunity. Blood cells that are part of the innate immune system include neutrophils, macrophages, eosinophils, basophils and NK cells.
- *Adaptive* (meaning adapting to external forces or threats) immunity — This type of immunity is provided by the thymus gland, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. B-cells and T-cells, the two main types of lymphocytes, carry out the adaptive immune response by recognizing and inactivating (disable) or killing invading organisms, either directly or by activating cells of the innate immune system. The adaptive immune system develops a memory of the invader, so that the next time the body is infected by the same invader, the immune response will develop more quickly and strongly.

What is Lymphoma?

Lymphoma is a type of cancer that originates from lymphocytes in the lymph nodes and other tissues in the lymphatic system. There are two major categories of lymphomas: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Each category is further subdivided into numerous types that differ in the type of cell they originated from (B, T, or NK cells), the way they develop and spread, and the way they are treated. Unlike other cancers, lymphoma therapy and prognosis (how well the patient will do) are determined by the lymphoma type, the presence of certain markers in lymphoma cells, and other factors like age and other medical issues, more than by the stage of the disease (how advanced the disease is).

Chapter 2: Seeking Medical Attention

This chapter explains the signs and symptoms of lymphoma and discusses how a doctor determines whether a person has the disease.

A *sign* is anything unusual that doctors, nurses, or physician assistants notice when they examine their patients or look at their test results.

A *symptom* is anything unusual in a normal body function, appearance, or sensation that a patient experiences. During a visit with a healthcare practitioner, patients should report all of their symptoms to their doctor, nurse, or physician assistant. Symptoms may indicate the presence of lymphoma or another disease.

What Are the Signs and Symptoms of Lymphoma?

Some patients with lymphoma do not have any obvious signs or symptoms of the disease at the time of diagnosis. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, lymphoma is discovered when symptoms occur and patients go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 2.1, lymphoma may cause different signs and symptoms depending on where it is located in the body. Keep in mind that these are only the most common signs and symptoms and many are not specific to lymphoma and may be due to other conditions.

Table 2.1. Signs and Symptoms Commonly Found in Patients

Sign or Symptom	Possible Reasons
■ Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin	■ Lymph nodes, or "glands," that swell when the lymphocytes respond to an infection or because of an increased number of abnormal lymphocytes.
■ Swollen, tender abdomen	■ Enlarged lymph nodes in the abdomen. ■ Accumulation (buildup) of fluid in the abdomen. ■ Enlarged liver or spleen.

Sign or Symptom	Possible Reasons
■ Abdominal pain, nausea, vomiting, decreased appetite, or feeling full more easily	■ Enlarged lymph nodes or an enlarged spleen pressing on nearby normal structures (for example, the diaphragm, nerves, or spine). ■ Enlarged spleen pressing on the stomach, which can make a person feel full after eating only a small amount of food. ■ Pain in the spleen. ■ Lymphoma in the intestine (or causing swelling near the intestine) possibly blocking bowel movements. ■ Lymphoma of the stomach or abdominal lymph nodes.
■ Constitutional symptoms (common symptoms in all NHL patients), including fevers for no known reason, unexplained drastic weight loss, and drenching night sweats that soak clothing and sheets (also called B symptoms)	■ Increased levels of inflammatory chemicals (substances that cause inflammation in the body) in the blood that are released by lymphoma cells or by the immune system.
■ Coughing, trouble breathing, or chest pain or pressure	■ Lymphoma in the chest, which may press on the windpipe or bronchi (tubes leading to the lungs). ■ Pleural effusion (fluid surrounding the lungs).
■ Headache, trouble thinking or finding words, weakness in extremities (legs or arms), loss of balance, personality changes, double or blurred vision, facial numbness, trouble speaking, or seizures	■ Lymphoma of the brain or spinal cord, or lymphoma originating in other parts of the body that has spread to or near the brain or spinal cord.
■ Shortness of breath, fatigue (extreme tiredness), pale skin, and easy bruising	■ A shortage of oxygen-carrying red blood cells (anemia) and thrombocytopenia.
■ Severe or frequent infections	■ Reduced ability to fight infection because of decreased numbers of certain types of white blood cells or low levels of gamma globulins.

When Should a Patient Seek Medical Attention?

Anyone who has an enlarged lymph node that does not return to normal size or continues to grow within one month, especially for lymph nodes outside the inguinal region (groin area) and/or persistent symptoms should see a doctor to make sure that lymphoma or another serious condition is not present. A good guideline is to seek medical attention if any of the signs or symptoms listed in Table 2.1 last longer than two weeks, or sooner if the symptoms are severe enough to impact a person's daily life. It is important to note that most patients with these symptoms do not have lymphoma, as diseases or conditions not related to lymphoma may cause many of these symptoms.

What Does The Doctor Look For?

During their visit, patients should describe all of their symptoms to the doctor. The doctor will ask questions about their medical history and perform a complete physical examination, during which the doctor is likely to:

- Ask details about symptoms including duration (how long), frequency (how often), intensity (how severe), and pain; these can be tracked in Lymphoma Research Foundation's mobile device app. (LRF's mobile app *Focus on Lymphoma* can keep track of symptoms and make communications with the doctor and healthcare team easier and more accurate. To learn more about this resource, visit our website at lymphoma.org/mobileapp, or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.)
- Measure blood pressure, pulse and other vital signs.
- Listen to the heart and lungs.
- Check the throat for enlarged tonsils.
- Look for any physical signs of infection or any other cancers, especially on the skin.
- Check for swollen lymph nodes under the chin, in the neck and tonsil area, above the shoulders, on the elbows, in the underarms, and in the groin.
- Examine other parts of the body to look for swelling or fluid that may be caused by swollen lymph nodes.

- Examine the abdomen to see whether the liver and/or spleen are enlarged and to feel for masses (lumps).
- Look for any weakness or *paralysis* (inability to make voluntary movements) that may be caused by an enlarged lymph node pressing against nerves or the spinal cord.

If the doctor suspects lymphoma after reviewing the symptoms reported and the signs discovered during the examination, additional tests will be requested to confirm the diagnosis.

Chapter 3: Diagnostic Procedures

Doctors need the results of various diagnostic tests (clinical tests used to identify a disease) to determine accurately whether a patient has lymphoma. This chapter explains the purpose of each test and describes what to expect during and after the test procedures. Before agreeing to any procedure, patients should make sure they understand the reasons for the procedure and what will be involved. Here is a list of questions patients may want to ask their doctor:

PATIENT TIP

Questions to Ask Before Having a Diagnostic Procedure

- Why is this procedure necessary?
- What will the procedure tell us about my condition?
- Can the same information be obtained in another way?
- What is involved in this procedure?
- What are the possible risks, complications, and side effects?
- Where will I have the procedure done?
- Will I have to do anything to prepare for the procedure?
- How long will the procedure take? Will I be awake? Will I feel pain?
- How long will it take for me to recover from the procedure?
- May someone else be present when I have the procedure?
- Will I need someone to take me home afterward?
- When will I get the results?
- When will we discuss the results?
- How will the results of this test affect my treatment?
- Will my insurance cover the procedure?
- What will my out-of-pocket costs (pay with one's own money) be?
- In case of receiving a dye, are my kidneys healthy enough to handle it?
- Will seafood allergies affect my tests?

How Is Lymphoma Diagnosed?

A tissue *biopsy* (see below) is the test required to establish an initial diagnosis of lymphoma. After that, one or more of the following tests may also be used to help with the diagnosis:

- *Immunophenotyping* of the cells collected from the biopsy (to describe the cells according to markers present on their surface).
- Genetic testing (to confirm the cytogenetic [the study of chromosomes and their abnormalities] results or to find out detailed information on genetic abnormalities in lymphoma cells). A chromosome is a thread-like molecule that contains the DNA (genetic material).
- Complete blood count (CBC) with *differential* (a blood test that counts the number of each type of blood cell and the amount of hemoglobin [the protein that carries oxygen in the blood]).
- Erythrocyte sedimentation rate (ESR) test. ESR measures how quickly red blood cells separate from the blood sample. Elevated ESR can be a signal of inflammation in the body.
- Comprehensive metabolic panel to check liver and kidney function.
- Testing for infection with the human immunodeficiency virus (HIV) and hepatitis B and C viruses.
- Imaging scans, like positron emission tomography (PET), computed tomography (CT) scans, or magnetic resonance imaging (MRI).

What Is a Biopsy?

A biopsy is a procedure in which a piece of the abnormal tissue is removed from the body and examined under a microscope. The information provided by this tissue sample is crucial to correctly diagnose the disease and to decide on the best course of treatment. A biopsy is the only way to confirm a lymphoma diagnosis.

Table 3.1 shows the three main types of biopsies used in patients with suspected lymphoma.

Table 3.1. The Three Main Types of Biopsies

Excisional or Incisional Biopsy	■ This type of biopsy is often considered the standard (method that is accepted and used by most doctors, and considered appropriate by experts) to establish an initial diagnosis of lymphoma because it allows the removal of bigger samples. The larger the sample, the more tissue can be examined, which improves the accuracy of the diagnosis. The additional tissue removed can also be used to perform other tests that may impact treatment. ■ A surgeon cuts through the skin to remove an entire lymph node (*excisional biopsy*) or a large portion of a lymph node or other tissue (*incisional biopsy*). ■ If the lymph node is close to the skin surface, the procedure can be done under local anesthesia (a local injection that numbs only the affected area). If the lymph node is in the chest or abdomen, the patient is sedated (the patient relaxes to the point of sleep but can wake up if needed to communicate) and the surgeon removes the tissue either *laparoscopically* (through a tube inserted in the body) or by performing more extensive (in a large physical area) surgery.
Core Needle Biopsy	■ This procedure is used when the lymph nodes being examined are deep in the chest or abdomen or in other locations that are difficult to reach with excisional biopsy, or when there are medical reasons for avoiding an excisional or incisional biopsy. ■ A large needle is inserted into the lymph node or other organ, and one or more small tissue samples are withdrawn using a syringe attached to the needle. This can generally be done under local anesthesia, and stitches are usually not required. ■ Rarely, the material collected may not be adequate (enough) for diagnosis, so a subsequent excisional or incisional biopsy may be necessary. ■ Often the core needle biopsy is guided by an imaging test, such as an ultrasound, CT scan, or PET scan. ■ It can also be used to check for lymphoma remaining, spreading or returning after treatment.
Fine Needle Aspirate (FNA) Biopsy	■ This procedure is performed with a very thin needle that is smaller than the kind used for a core needle biopsy. ■ Because of the small needle size, the sample only contains scattered cells, without preserving how the cells are arranged in the lymph node. Therefore, this test cannot provide enough information for a definitive initial diagnosis of lymphoma in the vast majority of cases. ■ An FNA biopsy may be used if another, more accurate biopsy is not possible. It can also be used to check for cancer spreading and *relapse* (return of the disease) after treatment.

After a tissue sample has been removed, it is examined by a *pathologist* (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples) under a microscope. A *hematopathologist* (pathologist who has undergone additional training in the diagnosis of blood diseases, including lymphoma) may also examine the sample. These specialists identify and classify the lymphoma cells by looking at their shape and size and how they are grouped in the sample using methods such as immunophenotyping (detailed below).

An *oncologist* (doctor who specializes in treating patients with cancer) or *hematologist* (doctor who specializes in treating patients with blood cancers and other blood disorders) uses the pathologist's report, along with results of other diagnostic tests, to confirm a diagnosis. If the pathologist's interpretation of the biopsy is uncertain, the biopsy should be reviewed by an expert hematopathologist.

Biopsies that are interpreted as "normal" may still contain lymphoma cells. This may occur when the sample is small and therefore it is not an accurate example of the rest of the lymph node. Sometimes a repeat biopsy is needed to establish the diagnosis. It takes an experienced hematopathologist working with the hematologist or oncologist to determine the need for more tissue sampling.

What is a CBC with a Differential Test?

In a CBC with differential test, samples of blood are examined to measure:

- The number of red blood cells.
- The amount of hemoglobin (the protein that carries oxygen) inside the red blood cells.
- The number of total white blood cells and the numbers of each type of white blood cell (neutrophiles, eosinophiles, basophiles, lymphocytes, and monocytes).
- The number of platelets.

The results of the CBC with differential assist in the diagnosis of lymphoma by ruling out (excluding) other types of blood cancer. The CBC with differential test is often repeated during the course of treatment to help

determine how much the treatment has affected the different blood counts and, in some cases, to help evaluate how well the treatment is working against the lymphoma.

What is Immunophenotyping?

Immunophenotyping is a process that can be used to distinguish (tell apart) among different types of cells (for example, normal lymphocytes vs lymphoma cells) based on the presence of antigens (proteins on the surface of certain cells). Antigens are specific to different cell types, just as landmarks are specific to different cities. Every antigen can be recognized by a specific type of antibody (protein produced by B-cells that binds to antigens and helps the immune system fight disease) that locks onto that particular antigen. Table 3.2 describes the immunophenotyping testing methods of flow cytometry and immunohistochemistry used in the diagnosis of lymphoma.

Table 3.2. Immunohistochemistry and Flow Cytometry Tests

Flow Cytometry	■ Cells from the biopsy sample are placed in a liquid solution and mixed with sets of antibodies that recognize antigens found in different types of lymphoma cells. ■ The cell-antibody mixture is injected into an instrument called a flow cytometer. This machine uses laser beams to detect the different colors of light the cells emit (produce) from the antibodies attached to them. This information is measured and analyzed by a computer and interpreted by a hematopathologist or another specialist.
Immunohistochemistry (IHC)	■ Thin slices of the biopsy sample (or thin layers of fluid) are treated with sets of antibodies that recognize markers found in different types of lymphoma cells and normal lymphocytes. ■ The pathologist examines the slides under a microscope to look for the visible color change that happens when the antibodies attach to the antigens. ■ The pathologist identifies and counts the number of cells that are highlighted by color (meaning that they have the antigen on their surface or inside the cell) with each of the different antibodies.

What are Chromosome Abnormalities?

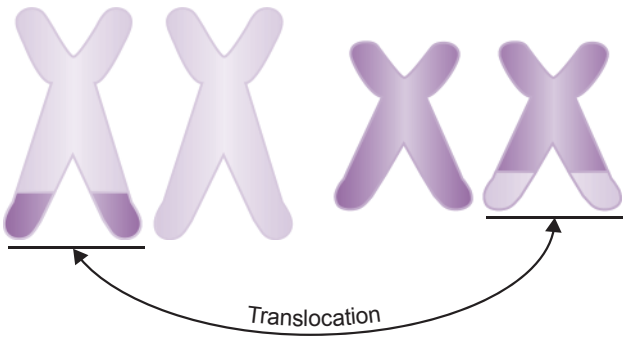
In every cell, DNA (genetic material) is wound up tightly into chromosomes. Normal human cells have 23 pairs of chromosomes. Some lymphoma cells have a different number of chromosomes (more or less than 23 pairs), or they may have abnormal chromosomes that have undergone a mutation (permanent change in the DNA). These changes can cause lymphoma cells to multiply uncontrollably. Some of the most common types of chromosome abnormalities that occur in lymphoma are described below.

Translocation

One type of chromosomal abnormality found in some types of non-Hodgkin lymphoma (NHL) is called a *translocation*, which occurs when parts of two different chromosomes break off and switch places with each other, as shown in the figure below. Some subtypes of NHL such as follicular lymphoma often or always carry a particular translocation.

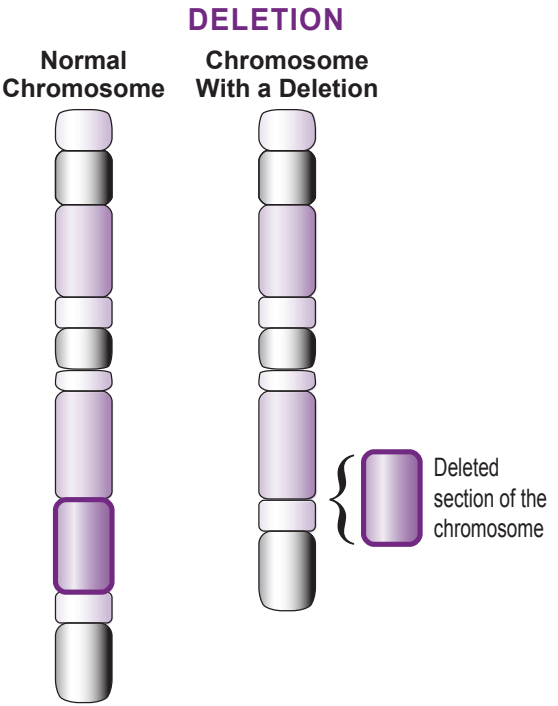
TRANSLOCATION

Two different chromosomes exchange portions of their genetic material



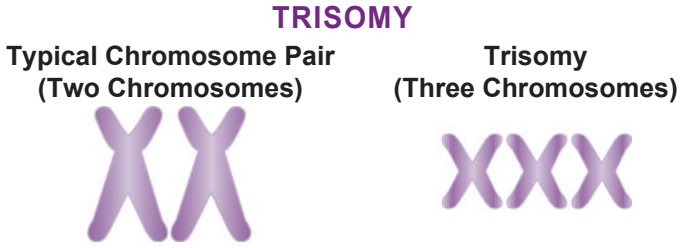
Deletion

Another type of chromosomal abnormality is called deletion, which happens when part of a chromosome is missing. Deletions are annotated (marked) using the abbreviation “del”, followed by the chromosome number and the location on the chromosome (“q” for the long arm, or “p” for the short arm) where the deletion has occurred. For example, deletions in chromosomes 11 [del(11q)], 13 [del(13q)], and 17 [del(17p)] are common in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).



Trisomy

Another type of chromosomal abnormality that may be present in the DNA of lymphoma cells is trisomy, which indicates the presence of an extra copy of a chromosome. The figure below shows the chromosomes as they look just before the cell divides. Normally, there are two pairs of each chromosome, but if a mistake occurs during cell division, a third copy of the chromosome can be created.



Types of Tests and Analyses for Detecting Chromosome and Genetic Abnormalities

Genetic tests examine specific sections of the DNA called genes to identify abnormalities present in lymphoma cells that may cause uncontrollable lymphocyte growth. A variety of tests are available to provide genetic information to better understand chromosome and genetic abnormalities in a patient or the subtype of disease present. Note that these tests aim to reflect the genetics of the cancer cells themselves, and not the genetics of normal cells, or the genetic material that is passed down from generation to generation. Examples of tests that are used to detect chromosome and genetic abnormalities are described in Table 3.3. These tests are important for learning more about a patient's particular disease and what treatments may be most effective for that patient.

Table 3.3. Types of Tests Used in Clinical Practice for Detecting Chromosome and Genetic Abnormalities

Fluorescence In Situ Hybridization (FISH)	■ FISH uses fluorescent chemicals that attach to certain parts of chromosomes to show the presence of translocations and other abnormalities. ■ FISH can be performed on samples of blood, lymph node tissue, bone marrow or other specimens. ■ The test results from FISH are usually available within a few days, which is quicker than the time required for cytogenetic testing.
Single-Nucleotide Polymorphism (SNP)	■ SNP uses fluorescent chemicals that attach to certain parts of DNA pieces to detect small abnormalities, and other mutations. ■ This method allows for the testing of a wide range of mutations called polymorphisms and is often used together with FISH.
Polymerase Chain Reaction (PCR)	■ A method to amplify (create several copies) DNA pieces to detect genetic abnormalities. ■ It may aid in doctors distinguishing between subtypes of CLL. It may also help establish diagnosis of various types of NHL when other test results are uncertain
Copy Number Variation Analysis	■ Detects whether there are extra or fewer copies of a given gene
Multiplex Next Generation Sequencing (NGS)	■ Collects the genetic sequence (the order of the units that form the DNA) for all DNA. It allows for several DNA sequences to be tested together to identify genetic changes that may contribute to disease. ■ Large sample numbers can be tested during one single experiment.

Doctors may use some or all of these tests to learn more about the genetics of a patient's lymphoma.

Other existing genetic tests that might be experimental and not currently used in clinical practice are described in Table 3.4.

Table 3.4. Other Types of Tests for Detecting Chromosome and Genetic Abnormalities

Genome Wide Association Study	■ DNA changes associated with a disease are identified and can be used to predict the presence of the disease
Whole Exome Sequencing	■ Collects the genetic sequence for all DNA that codes for proteins to identify genetic changes that may contribute to disease.
DNA Sequencing	■ Identifies variations (genetic changes such as mutations) in the DNA that could contribute to disease
RNA Sequencing	■ Identifies expression (the process that controls when and where proteins are made) levels of genes that can help identify abnormal patterns of expression that may contribute to disease.
Machine-Based Learning	■ A computer-based approach to analyze a large amount of genetic information and answer a variety of questions related to genes or genetic abnormalities

In recent years, genomics (the study of the entire set of genes and chromosomes in an individual) has helped doctors define subsets of patients within lymphoma subtypes based on their genetic profiles, which sometimes helps to make decisions about treatments. It is important for patients to discuss the interpretation of diagnostic tests with their doctor.

Chapter 4: Receiving a Diagnosis of Lymphoma

Receiving a cancer diagnosis can be overwhelming. It is perfectly normal to be shocked by the diagnosis, anxious about the future, and confused about the decisions that need to be made. This chapter will help patients and caregivers prepare for the start of treatment by explaining the next steps and providing tips for talking with doctors about any questions or concerns. Patients can also call the LRF's Helpline at (800) 500-9976 or email.

PATIENT TIP

First Steps to Take After Receiving a Diagnosis

- Take care of yourself (eat, sleep, rest, and exercise).
- Seek the support of family, friends, and others you trust.
- Learn about the disease and treatment options.
- Find medical care that meets your needs.
- Seek out additional sources of emotional and social support for people with cancer, such as LRF's Lymphoma Support Network that connects patients and caregivers with volunteers who have experience with lymphoma, similar treatments, or challenges.
- Research the cost of care, what your insurance will cover, and what financial assistance programs may be available to you.
- Maintain a copy of your medical records (paperwork, test results, and your own notes).
- Download and start using LRF's Focus On Lymphoma app on your mobile device to learn about and manage lymphoma.

A patient's primary care doctor usually makes a referral to a medical oncologist, hematologist, or hematologist/oncologist. Before agreeing to treatment by any specific doctor or treatment center, patients and caregivers should make sure that they feel comfortable with the healthcare team and the quality of care they provide. Patients of any age need to feel confident that the providers they select can meet their medical and personal needs.

PATIENT TIP

Questions to Ask to Select the Best Medical Team

- What are the credentials (proof of their qualifications) of the doctor, the other members of the medical team, and the hospital or cancer center?
- In the case of adolescent or young adults, does the treatment center have a designated adolescent or young adult program or at least appropriate support services and experience with this age group?
- Is the doctor board certified as a medical oncologist or hematologist? Has he or she passed qualifying examinations by the American Board of Internal Medicine (organization driven by doctors) to approve their competency (skills) in these specialties?
- Is the oncologist a lymphoma specialist or a general oncologist?
- How much experience do the doctor and treatment center have in treating patients with lymphoma in particular?
- How many patients with this type of lymphoma are being treated at this center now?
- Does the doctor and/or center participate in clinical trials?
- Does the clinic or center have modern surgical facilities (operation rooms and tools) and diagnostic equipment (machines and tools for testing patients for their disease)?
- Is the doctor or clinic associated with any major medical center or medical school?
- In case of an emergency, what arrangements are made for medical assistance after hours and on weekends?
- Is my health insurance accepted at this center? Will the treatment center file claims for reimbursement and process the paperwork?
- What kind of patient resources (such as disease education materials) does the clinic or cancer center have for patients with lymphoma?
- If I see other specialists (cardiologist, endocrinologist, etc.), will the doctor coordinate my cancer care with my other doctors?

Patients enrolled in a managed care health insurance program may have limited choices. However, patients have the right to choose another healthcare team if they are not entirely satisfied or comfortable with their first consultation visit. They should talk to other patients and caregivers about their experiences and ask them if they would recommend their doctor and healthcare team. Patients and caregivers who are not satisfied with their healthcare team should also share their concerns with their primary doctor and ask for a referral to a different doctor.

Mental Health Resources

While each experience is different, a lymphoma diagnosis often comes with mixed emotions. You may have a hard time trying to return to your routine as it was before you were diagnosed with lymphoma. For instance, some things you once did easily may now be challenging, or you may not have the same energy.

It is also very common for patients to feel anxious about the future and find it particularly hard not knowing what will happen next. While feelings of sadness and worry are normal and may even decrease over time, this can have a negative impact on your daily life. This can manifest in different ways, like trouble sleeping, changes in appetite, lack of interest in activities you previously enjoyed and inability to handle daily chores.

You may want to seek help from a trained counselor or a mental health professional if these symptoms last longer than two to three weeks. Mental health professionals can help you develop skills to reduce stress levels and cope with anxiety and depression. Complementary therapies such as acupuncture, meditation, and massage can also be beneficial in the management of the emotional effects of treatment.

Options for support networks to help navigate through this new stage are described on the next page.

Where Can I find Support?

Identify at least one person with whom you feel you can be honest about your feelings. You can open up to friends and family or join a support group for cancer survivors.

The LRF's one-to-one peer support program - Lymphoma Support Network - connects patients and caregivers with volunteers who have experience with lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. For more information about this program, please contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org, or visit lymphoma.org/resources/supportservices/lsn.

Maybe you can find assistance with patient organizations offering support such as Cancer Care (call 800-813-4673) or visit cancercare.org/support_groups) and the Cancer Support Community (call (888) 793-9355 or visit cancersupportcommunity.org). For some individuals, faith and spirituality is the best route to find comfort. Some members of your place of worship may help you cope with your concerns, such as feeling alone, fear of death, searching for meaning, and doubts about faith. As mentioned earlier, speaking with a mental health professional can also be very helpful.

There are many options available, and it is important that you choose the one that is right for you. Having a reliable support network can provide a means to work through your negative emotions and help you cope with physical effects of treatment or deal with aspects of daily life (like family, school or work responsibilities). Follow-up care can also include home care, occupational or vocational therapy (therapy that helps patients returning to work following an injury or disease), pain management or physical therapy.

Chapter 5: Work-Up Before Treatment Can Begin

After the initial diagnosis of lymphoma, the doctor may order other tests such as blood tests, genetic tests, imaging studies, heart and lung function tests, a bone marrow biopsy, and, less frequently, additional biopsies. This process is often called the *work-up* or *staging* studies. Some of these tests are needed to determine a person's disease stage - a measure of whether and how much the disease has spread to other parts of the body. Other tests check how the disease has affected a person's overall health and major organ functions. Together, these test results provide the information needed to help patients and their doctors decide on the best course of treatment. This chapter explains the reasons for the various tests, how these tests work, what to expect, and how lymphoma is staged.

What Evaluations Are Used in the Work-Up for Lymphoma?

Patients with lymphoma may undergo some or all of the following work-up tests before starting treatment. Many of these tests may be repeated during treatment.

- Physical examination with special attention to the size of the lymph nodes, liver, and spleen.
- Determination of general health status (also called *performance status* or *functional status*) to see how well a patient feels and how well they can carry out normal daily activities, such as getting washed and dressed, going to work, and doing chores.
- Identification of any *comorbidities* (other health problems besides lymphoma that patients may already have), such as diabetes, heart disease, or chronic lung disease, that could affect the choice of lymphoma treatment and the response to treatment.
- Questioning about the presence of fever, night sweats, weight loss, chills and itching (also called "B symptoms").
- Complete blood count with differential.
- Blood tests to measure levels of beta-2 microglobulin (a prognostic marker [helps predicting the likely course of a disease]),

lactatedehydrogenase (LDH) (which is found in high levels in the blood of many patients with fast-growing tumors), and uric acid (which builds up in the blood due to the death of cancer cells and causes damage to the kidneys and other organs).

- Measurement of ESR.
- Testing for infection with HIV, hepatitis viruses, and other viruses.
- Measurement of levels of an antibody called immunoglobulin G (IgG) that helps fight infections.
- Reticulocyte count (to determine how fast the bone marrow is making red blood cells), and haptoglobin (to determine if red blood cells are being destroyed in the vascular system [network of arteries, veins, and capillaries that supplies blood to the tissues of the body]).
- Comprehensive metabolic panel which tests kidney and liver function.
- Pulmonary studies to evaluate lung function.
- CT and/or positron emission tomography-CT (PET-CT) scans of the neck, chest, abdomen, and pelvis. In general, the results of these imaging tests are the most important when determining the stage of lymphoma.
- Echocardiogram (ECHO) or multigated acquisition (MUGA) scan to evaluate heart function.
- Magnetic resonance imaging (MRI) is often used for suspected bone or nervous system (including brain) involvement.
- Excisional, incisional, or core needle biopsy (see Table 3.1 in Chapter 3 for more information about biopsies).
- Bone marrow aspiration and/or biopsy.
- Advanced diagnostic testing for chromosomal or genetic changes.
- Lumbar puncture (detailed in Table 5.2. below).

What Types of Imaging Tests May Be Used?

A doctor will order imaging tests to help identify areas of the body where the lymphoma has spread, and, later on, to determine how well treatment is working. Most of these tests are painless and require no anesthetic. Several types of imaging procedures (described in Table 5.1) may be needed to thoroughly evaluate the extent of disease.

Table 5.1. Types of Imaging Tests

Computed Tomography (CT) Scan	■ A CT scan takes X-rays from many different angles around the body. A computer combines the pictures obtained from these different angles to give a detailed image of organs inside the body. ■ Patients with lymphoma often have CT scans of the neck, chest, abdomen, and pelvis to find out how many lymph nodes are involved and how enlarged they are, as well as whether any internal organs are affected by the disease. ■ Before a CT scan, the patient may be asked to drink a contrast liquid and/or receive an intravenous (IV; liquid that is infused directly into a vein) injection of a contrast dye that will more clearly outline any abnormal areas in the body.
Magnetic Resonance Imaging (MRI)	■ An MRI uses magnets and radiofrequency waves to acquire images from different angles throughout the body. MRIs do not involve the use of radiation. ■ An MRI can provide important information about tissues and organs, particularly the bones and nervous system that is not available from other imaging techniques, but it is also less helpful in other areas such as the lungs. ■ Patients may receive IV contrast for MRIs, similar to CTs, but this contrast is made of a different substance. Patients who have an allergy to CT contrast, shellfish, or iodine can take MRI contrast. ■ MRI scans cannot replace CT scans, because they do not provide clear images of lymph nodes as well as CT scans do.
Positron Emission Tomography (PET)	■ A PET scan evaluates lymphoma activity in all parts of the body. ■ Radioactive fluorodeoxyglucose (a type of sugar) is injected into the body. A positron camera is then used to detect radioactivity and produce cross-sectional (information collected from many different sections of the body) images of the body. This test relies on the fact that cancer cells metabolize (consume) sugar faster than normal cells, so that more consumption on a PET scan indicates more metabolic activity, suggesting the presence of the malignant (cancer) cells. ■ While CT scans provide information about the size of a lymph node, PET scans can better indicate whether the lymph node contains active lymphoma cells. ■ PET scans help distinguish growing tumors from an old injury or scar tissue (a mark left on the skin or body tissue while healing from an injury) and may be used to assess a patient's response to treatment. ■ PET and CT scans are often combined into a single test (PET-CT), in which the CT procedure is slightly modified (changed) from that described above.

Why Might Another Type of Biopsy Be Needed?

Once the lymphoma diagnosis is made, the doctor may order other types of biopsies for additional pathology studies to see whether the disease has spread to other parts of the body (see Table 5.2).

Table 5.2. Other Types of Biopsies

Bone Marrow Aspiration and/or Biopsy	■ Bone marrow is the soft, spongy material found inside bones. ■ Lymphoma can spread to the bone marrow or start in the bone marrow. ■ A bone marrow aspiration and biopsy may be done to determine the amount of disease in the bone marrow. ■ For the aspiration part of this procedure, the doctor cleans and numbs the skin over the hip, inserts a thin, hollow needle into the hip bone, and removes a small amount of liquid from the bone marrow using a syringe. ■ A bone marrow biopsy is often performed immediately after the aspiration and removes a piece of bone. ■ Although these procedures may be done without anesthesia some centers offer light sedation based on patient and doctor preference.
Lumbar Puncture (Spinal Tap)	■ This procedure is used to determine whether the lymphoma has spread to the cerebrospinal fluid (CSF), the liquid that surrounds the brain and spinal cord. ■ This test is only used for patients with certain types of lymphoma or for those who have symptoms suggesting that the disease has reached the brain. ■ After numbing a small area of the lower back with a local anesthetic, the doctor uses a thin needle to remove a sample of fluid, which is sent to a laboratory for analysis.
Pleural, Pericardial, or Peritoneal Fluid Sampling	■ This procedure is used to determine whether the lymphoma has spread to the lining of the chest or abdomen, where it can cause fluid to accumulate. ■ The doctor numbs the skin with a local anesthetic, inserts a small needle, and uses a syringe to remove a sample of the fluid for laboratory analysis. ■ The fluid is called pleural fluid when found inside the chest, *pericardial* fluid when found surrounding the heart, and *peritoneal* fluid when found inside the abdomen.

What Is Performance Status?

Performance status (PS) is a numerical rating of patients' general health and their ability to carry out normal daily activities (such as getting washed and dressed, going to work, and doing chores). Measurement of PS helps doctors determine which treatments a patient should get and how well the treatment is working; it also affects the eligibility for clinical trials. As shown in Table 5.3, PS can be graded using the Eastern Cooperative Oncology Group (ECOG; scientific organization that conducts cancer research) PS on a scale of 0–4, with the lower numbers indicating better health. Some institutions may prefer the Karnofsky PS, which uses a scale of 0-100, with higher numbers indicating better performance. Note that in younger patients, other PS scales may be used.

Table 5.3. The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	■ Fully active and able to carry on all pre-disease activities without restriction.
1	■ Cannot perform taxing (demanding) physical activities but can move around (ambulatory) and carry out light work (such as light housework) or do things that can be done while seated (such as office work).
2	■ Can move around and take care of oneself, but unable to do any work; up and about for more than half of awake hours.
3	■ Can only partially take care of oneself; confined to a bed or chair for more than half of awake hours.
4	■ Completely disabled; cannot take care of oneself; completely confined to a bed or chair.

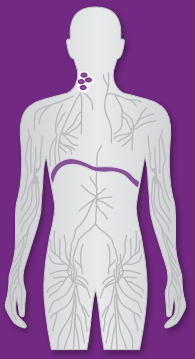
How is Lymphoma Staged?

Staging is used to describe how widely the lymphoma has spread. Doctors use the stage of disease, along with test results and other factors, to decide the best time to begin treatment and what treatments are likely to be the most effective for each patient.

Patients with Non-Hodgkin Lymphoma (NHL; except Chronic Lymphocytic Leukemia [CLL] and Small Lymphocytic Lymphoma [SLL]) and Hodgkin Lymphoma (HL) are staged using the Ann Arbor and Lugano systems. For adults, there are two main divisions of lymphoma (limited and advanced disease) and four stages designated by Roman numerals I through IV. Stages I and II are considered limited disease, although Stage II may be considered advanced in patients with bulky disease (tumors greater than 10 centimeters [~4 inches] wide). The presence of bulky disease is usually noted by adding the letter X to the stage. Stages III and IV are considered advanced disease. Although some patients have advanced lymphoma at the time they are diagnosed, their disease can often be successfully treated.

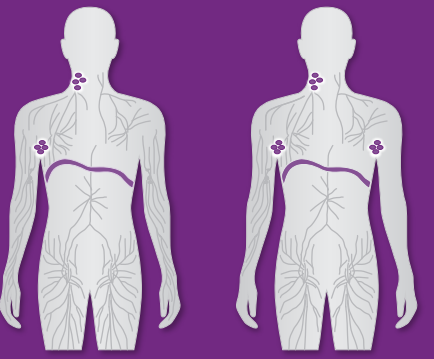
The Ann Arbor staging system has traditionally been used for staging lymphoma. Although this older staging system is still in use, a modification of the Ann Arbor staging system called the Lugano Classification was proposed in 2014. This system is shown in the figure on the next page.

STAGING OF LYMPHOMA (LUGANO CLASSIFICATION)



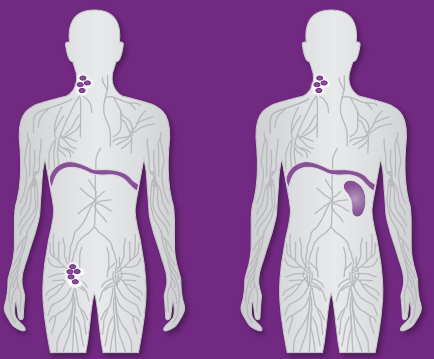
Stage I:

- Involvement of a single lymph node or group of adjacent nodes



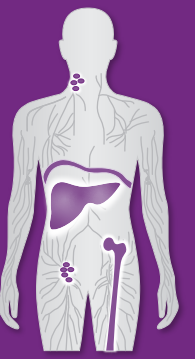
Stage II:

- Involvement of two or more groups of lymph nodes on the same side of the *diaphragm* (muscle that separates the chest from the abdomen)



Stage III:

- Involvement of lymph nodes on both sides of the diaphragm, or
- Involvement of lymph nodes above the diaphragm plus spleen involvement



Stage IV:

- Widespread disease in lymph nodes, bone marrow, and organ involvement, such as liver or lungs

Stage I–IV lymphoma can be further classified based on whether "B symptoms" (fever, unexplained weight loss of greater than 10 percent

of body weight, and drenching night sweats) are present. An "A" designation means that the patient does not have "B symptoms," while the "B" designation means that the patient does have "B symptoms" (see Table 2.1 in Chapter 2 for additional discussion of "B symptoms").

In children, lymphoma is staged using a different system in which the lymphoma is classified as low-, intermediate-, or high-risk.

How is CLL/SLL Staged?

Because CLL/SLL is almost always widely spread through the body, a different staging system is used. Patients with CLL are staged using either the Rai staging system or the Binet classification system. Doctors in the United States tend to use the Rai system (Table 5.4), while the Binet system (Table 5.5) is more popular in Europe. Rai staging establishes risk groups (low, intermediate and high) that indicate the likelihood that the disease may worsen or require treatment. Both staging systems are designed to assess the quantity of the disease present and whether the disease is considered active or progressing (when the tumor is growing and/or spreading). It is important to note that patients with CLL/SLL do not necessarily progress through stages in order.

Table 5.4. The Rai Staging System for CLL/SLL

Grade	Description	Risk Group
0	■ Blood lymphocytosis (increased lymphocytes). ■ No lymph node enlargement, anemia (decreased red blood cells) and no thrombocytopenia (decreased platelets).	Low
I	■ Blood lymphocytosis and enlarged lymph nodes. ■ No anemia and no thrombocytopenia.	Intermediate
II	■ Blood lymphocytosis and enlarged spleen (splenomegaly) and/or enlarged liver (hepatomegaly). ■ No anemia and no thrombocytopenia.	Intermediate
III	■ Blood lymphocytosis. ■ Anemia (hemoglobin less than 11 grams per deciliter).	High
IV	■ Blood lymphocytosis. ■ Thrombocytopenia (platelets less than 100,000 per microliter).	High

Table 5.5. The Binet Staging System for CLL/SLL

Grade	Description	Match-Up with Rai Stages
A	■ Less than three of five possible enlarged areas* ■ No anemia and no thrombocytopenia	Rai stages 0, I, and II
B	■ Three or more of five possible enlarged areas* ■ No anemia and no thrombocytopenia	Rai stages I and II
C	■ Any number of possible enlarged areas ■ Anemia and/or thrombocytopenia	Rai stages III and IV

*The five possible palpably enlarged areas are the cervical (neck) lymph nodes, the axillary (underarm) lymph nodes, the inguinal (groin) lymph nodes, the spleen, and the liver.

How is Treatment Determined?

The doctor will discuss the risks, benefits, and side effects associated with the different treatment choices applicable to the patient's particular situation. Patients and caregivers should share questions and concerns with the doctor so that together they can decide which option is best. It is always helpful for patients to write down their questions and go over them with their treating physician and/or healthcare team. The following questions can be used to guide the conversation and help patients make an informed decision.

PATIENT TIP

Questions to Ask Before Treatment Begins

- What is my exact diagnosis? What subtype of lymphoma do I have? May I have a copy of the report from the pathologist?
- What is the stage of my disease? In what area of the body is it specifically located?
- What are my prognostic factors, and what does that mean?
- What are my treatment choices? Which do you recommend for me and why? Would choosing one treatment prevent me from getting a different kind of treatment later on? How are the different treatments administered?

Questions to Ask Before Treatment Begins *(continued)*

- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of lymphoma? Would a clinical trial be appropriate for me? How would I benefit? Are there any drawbacks of participating in a clinical trial?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- What are the risks and possible side effects of each treatment? Can these side effects be prevented or controlled?
- What should I do to take care of myself during treatment?
- Are there any late (appear only months, years or decades after treatment has ended) or long-term (occur during treatment and continue for months or years) side effects I should be aware of?
- Will treatment impact my fertility or ability to have children in the future? Is there time for sperm banking/egg harvesting before starting treatment?
- How long will the treatment last?
- What are the chances the treatment will be successful?
- How will the treatment affect my normal activities (for example, work, school, childcare, driving, sexual activity, and exercise)?
- Is there anything my caregiver needs to do to prepare to care for me while I undergo treatment?
- Will I be able to work during treatment? Will I be able to drive or take public transportation during my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- How much will the treatment cost? Will my insurance cover some or all of it? What will my out-of-pocket costs be?

When to Get a Second Opinion?

Before starting any type of treatment, a patient may want to consider getting a second opinion, especially if the diagnosis is rare, complicated, or uncertain. The purpose of the second opinion is not to question the doctor's expertise but to make sure the suggested treatment plan is the best choice for the patient's particular case, as well as to evaluate alternative treatment options, including clinical trials. Physicians, like everyone else, have opinions regarding which treatment is best for an individual patient and each patient should hear other physicians' opinions. Inform your treating physician if you are seeking a second opinion.

Most doctors are supportive and helpful if patients tell them they would like to get a second opinion. Patients should ask the doctor if it is safe to briefly delay the start of treatment to provide the time needed to get a second opinion. Some insurance programs require second opinions, and others may pay for a second opinion if a patient or doctor requests it.

When getting a second opinion, patients might want to consider the tips outlined below.

PATIENT TIP

Getting a Second Opinion

- Most hematologists/oncologists/lymphoma specialists associated with medical schools or cancer centers may be willing to provide a consultation and work together with a local oncologist to provide treatment and follow-up care.
- As part of the second opinion, another pathologist must review the tissue and blood samples to confirm the diagnosis. The pathology of lymphoma is often complex, and some pathologists may have limited experience analyzing lymphoma cells, so it is valuable to have the pathology results reviewed by an expert hematopathologist with extensive experience in lymphoma. In addition, it is essential to review radiology studies including CT scans and PET scans.

Getting a Second Opinion *(continued)*

- To get a second opinion, you will need to provide the consulting doctor with a complete copy of all medical records, pathology samples, images and scans, and reports. When you set up the appointment, ask the office for a list of the materials you need to bring. It will be useful to keep your own copy of all these records in case you have questions or concerns later on.

To identify lymphoma specialists to contact for a second opinion:

- Ask your current doctors, family members, other patients, friends, and coworkers.
- Contact the patient referral service at your local hospital and at the nearest hospital associated with a medical school; many hospitals have online directories that can be searched to find a specialist in your area.
- Visit LRF's website at www.lymphoma.org or contact the LRF Helpline by phone (800-500-9976) or email (helpline@lymphoma.org). However, note that LRF does not provide a physician referral service.
- Visit the American Society of Clinical Oncology (ASCO) website at www.cancer.net to search their oncologist database.
- Visit the American Society of Hematology (ASH) web page at www.hematology.org/patients to search for hematologists with expertise in lymphoma.
- Visit the American Board of Medical Specialties (ABMS) Certification Matters website at www.certificationmatters.org to find out if doctors are board certified in a particular specialty.

How to Communicate with the Healthcare Team?

Patients and caregivers can ease some of their anxieties by establishing open, honest communication with their healthcare team regarding their diagnosis and treatment. This can help patients and caregivers better

understand the treatment regimen, including how it works, what tests are involved, and what side effects and complications may be associated with it.

A good first step is to write down all questions that come to mind. Before meeting with a doctor, nurse, or physician assistant, patients should consider organizing their questions into a list to bring to the visit. Since time with doctors, nurses, and physician assistants may be limited, patients should put the two or three most important questions at the top of their list. However, it is also important that a member of the patient's medical team reads through all the questions, because some may be more important than the patient realizes. LRF's mobile app, *Focus On Lymphoma*, can save and organize your list of questions to review with your healthcare team. For assistance with preparing questions to ask your healthcare team, contact the LRF Helpline at (800) 500-9976 or email helpline@lymphoma.org.

Patients should consider having a family member or close friend accompany them to the doctor's office or clinic to help ask questions and understand and remember answers. This person could also help by taking notes during the visit. Some patients bring a recording device or a phone or tablet to record the discussion. LRF's *Focus On Lymphoma* mobile app enables you to record your session with your doctor. Patients should ask the doctor, nurse, or physician assistant for permission before recording any conversations.

Oncology nurses are often well informed about cancer treatments and are an excellent source of information on a wide range of topics. Additionally, oncology social workers are available to assist with practical, emotional, and other support needs throughout the diagnosis and treatment process.

Although family members are often very concerned about their loved ones and want information concerning their care, confidentiality (privacy) rules prohibit doctors from giving out information to anyone without the patient's permission. **For efficiency, one family member should be chosen as the family contact, and the healthcare team should know that person's identity and contact information.** Most importantly, it is essential for patients and their caregivers or family contact person to have the names, addresses, office numbers, and emergency contact information

of the physicians involved in their care, so that they can communicate with the oncologist or hematologist regularly or in the event of an emergency. Adding these phone numbers directly to a cell phone may be helpful so patients or caregivers have the numbers directly on hand, if needed.

Open communication between patients and doctors is essential. The tips below can be used to help patients better communicate with their healthcare team. For assistance with communicating with your doctor, contact the LRF Helpline at (800) 500-9976 or email helpline@lymphoma.org.

PATIENT TIP

Communicating With Your Doctors

At home:

- Know your medications.
- Keep a journal of your symptoms to help you remember the details you want to discuss with your doctor during your next office visit.
- Ask your doctor or nurse ahead of time which symptoms need to be communicated to them immediately and which can wait for your next visit.
- If your questions are urgent, do not wait for the next office visit; call the doctor's office to discuss your concerns.
- Ask whether your healthcare team has an online "patient portal." These portals may provide secure email contact and educational materials, and they often allow patients to check benefits (compensations that might be provided by the state) and coverage (what costs are covered by your health insurance), schedule non-urgent appointments, and order prescription refills.
- Visit lymphoma.org/mobileapp to download the Focus On Lymphoma mobile application (app) from LRF to help you plan appointments, manage medications and blood work, document treatment side effects, record doctor visits, and list questions.

Communicating With Your Doctors *(continued)*

At your next doctor's visit:

- Bring your symptom journal and list of questions to discuss with your doctor or nurse.
- Bring a list of the medications you are currently taking, including the dosage and frequency.
- Ask a family member or friend to come with you to provide emotional support and take notes.
- Do not be afraid to ask questions if you do not understand something. Your doctor will want to know if you are uncertain or confused and will be happy to address your concerns.
- Ask about whom should be contacted for specific questions and how you can reach them on weekends or evenings.
- Ask whether members of your healthcare team communicate electronically (by email, patient portals, etc.). Some healthcare providers (individual doctors or healthcare organizations such as clinics or hospitals) do not use electronic forms of communication with patients because of concerns about security and patient privacy.
- Make sure you understand the next steps in your care before you leave the doctor's office.
- Request written information that you can take home to help you remember everything your doctor tells you.

How to Be a Self-Advocate?

Being a self-advocate and an active participant in healthcare decisions can be a positive experience. It may help patients regain a sense of control that they may have lost following the lymphoma diagnosis by making sure patients receive the best care. Patients and caregivers should remember they are partners in their treatment plan. Patients should ask questions, learn about options, and work closely with their healthcare team. Physicians should be comfortable with patients asking questions.

It is important for patients to be comfortable with the doctors and the approaches they take. If patients or caregivers are not comfortable, they should openly discuss their concerns. Confidence in the medical team often leads to confidence in treatment. If patients feel that the team is not a good match, they should ask for a referral to a different healthcare team.

Although each patient is different and each response to therapy is unique, knowing someone who has been through the same situation and who may have had similar concerns can be a source of great comfort. If patients or caregivers are interested in talking to and learning from people who have had similar experiences, they can ask their healthcare team members about any support groups in the area or contact LRF for more information about the one-to-one peer support program *Lymphoma Support Network*.

Finally, it is important that patients not be afraid to talk with the healthcare team about nonmedical issues such as transportation, finances, insurance, working through treatment or taking time off, and childcare. The tips below offer self-advocacy strategies for patients.

PATIENT TIP

Self-Advocacy

- Do not be afraid to ask your doctors or nurses questions about your care. An educated patient asking questions is not 'being a challenge to your physician' (or 'being a difficult patient').
- Learn more about lymphoma by asking your doctor for information and visiting reliable websites, such as LRF at www.lymphoma.org.
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor's office, cancer center, or hospital.
- Consider joining LRF's Lymphoma Support Network, a nationwide peer support program that matches patients and caregivers with people who have had similar experiences. For information about the program, call (800) 500-9976 or email helpline@lymphoma.org.

Adolescents and Young Adults

Adolescents and young adults (AYAs) ages 15 to 39 years are more likely to be diagnosed with lymphoma than younger children. The young age and maturity level of AYAs has a significant effect on their ability to manage their diagnosis and treatment. Factors such as the belief that "it cannot happen to me," overall healthcare-related knowledge, unique concerns regarding body image and fertility issues, and relationship matters must all be considered when building a treatment plan for AYAs. Additional issues such as health insurance questions, potential financial hardships, and peer concerns must all be managed carefully.

There are many programs offered at cancer centers throughout the United States to help AYAs receive expert care for their disease and offer support for psychosocial and fertility/sexual health concerns. AYAs and their caregivers might want to consider the tips given below.

PATIENT TIP

Special Considerations for Adolescents and Young Adults

- It is critical to seek appropriate medical care instead of depending on internet platforms or social media as a primary source of information about their symptoms.
- It is important to try to overcome feelings of discomfort when discussing questions and concerns about a diagnosis, treatment, side effects, or even topics like sexuality with the doctor or healthcare team. Communication between patients and their doctors is extremely important and is always kept confidential.
- Some AYAs may feel more comfortable having their parents present during appointments, while others may prefer to speak with their doctors alone. It is also okay to ask their doctor about seeking a second opinion about their disease and/or treatment.
- It is a good idea for AYAs to speak with their doctors and healthcare team before treatment about what kinds of physical changes to expect so they are fully prepared if these changes arise.

Special Considerations for Adolescents and Young Adults *(continued)*

- AYAs and their caregivers are strongly encouraged to keep copies of all medical records by using the Lymphoma Care Plan document available on the Lymphoma Research Foundation's (LRF's) website at www.lymphoma.org/publications.
- It is important for AYAs to keep an open line of communication with their parents. However, many AYAs find people their age with cancer may be able to provide unique insights (understanding) and support. Many people also benefit from speaking with a therapist or counselor trained in cancer.
- Issues with fertility (ability to have children) should be discussed with the healthcare team at the time of diagnosis, because AYAs can take steps to preserve (keep) their fertility before their lymphoma treatment begins.
- Meeting with academic advisors or school administrators can help clarify the best course choices to complete educational goals. Federal laws allow students with disabilities (mental or physical condition that limits physical or sensation activities) to receive special accommodations (e.g., extended time to complete tests, audio textbooks, free tutoring, or modified housing).
- AYAs should consider arranging a meeting with their workplace's human resources representative to discuss possible and appropriate accommodations before and after treatment.
- Young adults in general are at risk of being uninsured. A provision of the Patient Protection and Affordable Care Act allows young adults to remain on their parent's health plans until the age of 26 years. Visit www.healthcare.gov/young-adults/ for more information. The Samfund provides support through direct financial assistance and free online support and education (www.thesamfund.org/).

Chapter 6: What to Know Before Starting Treatment

What Are Prognostic Factors?

The characteristics that help predict a patient's prognosis (prediction of the likely course of a disease) are called *prognostic factors*. Favorable or good prognostic factors tend to be associated with better outcomes (overall longevity or good response to treatment), while unfavorable prognostic factors tend to be associated with worse outcomes.

To help doctors determine the best course of treatment, patients with lymphoma are grouped in prognostic categories reflective of their risk factors. Some of the adverse prognostic risk factors are listed in Table 6.1 and are derived from the International Prognostic Score, a model commonly used for HL and some forms of NHL. Note that the risk factors are somewhat different in pediatric patients. Keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do (not what will happen to an individual patient). The doctor most familiar with the patient's situation is in the best position to interpret the increased risk, understand how it applies to a patient's particular situation, and respond to any questions you might have.

Table 6.1. Adverse Prognostic Risk Factors

Stage	Adverse Prognostic Risk Factors
Limited Disease	■ 60 years or younger. ■ *Bulky disease* (a tumor in the chest larger than one-third of the width of the chest, or a tumor at least 10 centimeters or 4 inches wide). ■ Cancer that has spread directly outside the lymph nodes to an adjacent site. ■ ECOG score ≤ 1 (patient able to function normally). ■ A high ESR: over 30 in someone with B symptoms, or over 50 for someone without B symptoms. ■ Abnormal levels of LDH. ■ Cancer in three or more nodal areas. ■ The presence of "B symptoms" (fever, weight loss, and night sweats).
Advanced Disease	■ Male. ■ 45 years or older for HL, and older than 60 years for NHL. ■ Stage IV disease (lymphoma is in two or more organs outside of the lymph nodes). ■ Low blood albumin (a type of protein) level (less than 4 grams per deciliter). ■ Low hemoglobin level (less than 10.5 grams per deciliter) ■ High white blood cell count (15,000 cells per microliter or greater). ■ LDH above the upper limit of normal. ■ Low lymphocyte count (fewer than 600 cells per liter, or fewer than 8 percent of the total white blood cell count).

What is Decreased Blood Cell Production?

The bone marrow constantly produces red blood cells, white blood cells, and platelets. Several types of therapies for lymphoma temporarily interfere with the ability of the bone marrow to produce enough of one or more of these different types of blood cells. This is called *myelosuppression*. For this reason, chemotherapy is given in treatment cycles every 2 to 4 weeks (usually every 3 weeks), so that the body can recover from myelosuppression and other side effects.

To prevent and monitor myelosuppression, samples of a patient's blood are tested with a CBC with differential, which measures the numbers of red blood cells and platelets, as well as all the different subtypes of white blood cells. These tests are usually done before and sometimes during the treatment process. Table 6.2 describes five of the most common conditions involving a decrease in blood cell production.

Table 6.2. Five Common Conditions Caused by Decreased Blood Cell Production

Anemia	■ *Anemia* is a decrease in the number of red blood cells. ■ The most common marker of anemia is a low level of hemoglobin (protein present in red blood cells that is responsible for transporting oxygen). ■ Many chemotherapy drugs cause mild or moderate anemia. ■ Anemia can make people feel tired and short of breath, especially when it is severe. ■ Although seldom needed, drugs or red blood cell transfusions (a procedure in which donated blood is given intravenously to a patient can be used to treat severe anemia.
Leukopenia	■ *Leukopenia* refers to a decrease in the number of leukocytes, or white blood cells. Leukocytes include lymphocytes (B-cells and T-cells), neutrophils, basophils, eosinophils, and monocytes. ■ Patients with low levels of neutrophils and lymphocytes are at increased risk of infections.
Lymphopenia	■ *Lymphopenia*, also called lymphocytopenia, refers to a decrease in the number of lymphocytes. Lymphocytes produce antibodies that fight bacterial and viral infections. About 20 to 40 percent of white blood cells are lymphocytes. ■ Patients with low levels of lymphocytes (notably neutrophils [see below]) are at increased risk for infections.

Neutropenia	■ *Neutropenia* refers to a decrease in neutrophils, the primary type of white blood cells that fight bacteria or other infections. ■ Patients with low neutrophil counts are at higher risk for serious and even life-threatening infections. Symptoms of infection include fever and chills. ■ During chemotherapy, doctors regularly monitor the patient's *absolute neutrophil count* (ANC), the number of neutrophils in the peripheral blood. Because patients with an ANC below 500 cells per microliter are at particularly high risk for infections, doctors may decrease the chemotherapy dosage or delay the next treatment until the ANC returns to 500 or greater. ■ Some patients require treatment with antibiotics and hospitalization to prevent or treat infections. ■ To avoid a patient missing a dose of chemotherapy, doctors sometimes prescribe drugs like filgrastim (Neupogen, Granix, Zarxio) and pegfilgrastim (Neulasta) to reduce the time and intensity of neutropenia. These drugs can sometimes cause bone pain, which is usually temporary. Bone pain in the chest can simulate (imitate) heart disease; patients experiencing unexplained chest pain should seek medical attention immediately. ■ Unless contraindicated (not recommended), bone pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil and others) or naproxen (Aleve, Naprosyn), the antihistamine loratadine (Claritin, Alavert) or the analgesic acetaminophen (Tylenol).
Thrombocytopenia	■ Thrombocytopenia refers to a decrease in the number of platelets in the blood. Platelets help start the clotting process when bleeding occurs. ■ Patients with low platelet counts may bruise easily; have cuts that bleed more or longer than usual; have nosebleeds or bleeding gums; or bleed from places that have not been injured. ■ A platelet transfusion may be needed if thrombocytopenia is severe or if the patient develops bleeding.

What Terms Do Doctors Use to Describe Treatment and Its Outcomes?

Doctors who treat patients with lymphoma use certain terms to describe a patient's treatment and the expected outcomes. Some of these terms are defined in Table 6.3.

Table 6.3. Terms Used to Describe Treatment and Its Outcomes

Cure	This word is used cautiously by doctors for subtypes of lymphoma that are potentially curable when there are no signs of the lymphoma reappearing after many years of continuous complete remission.
Complete Remission (CR)	This term is used when all signs of lymphoma have disappeared after treatment. It does not mean that the lymphoma is completely cured; rather, it indicates that the symptoms have disappeared, and the lymphoma cannot be detected using current tests (such as CBC or imaging methods). Relapses can occur in patients who experience CR. If complete remission is maintained for a long period, it is called a *durable remission*. A complete remission is a necessary first step for cure.
Partial Remission (PR)	This term is used if a lymphoma tumor has responded to treatment and shrunk to less than one-half of its original size.
Minor Response (MR) or Minor Improvement	This term is used if a lymphoma tumor has shrunk following therapy but is still more than one half of its original size.
Minimal Residual Disease (MRD)	This refers to the small number of cells that remain in the blood or bone marrow after the completion of treatment.
Stable Disease	This term means the disease has not gotten worse or better following therapy.
Disease Progression	This term means the disease has worsened or the lymphoma has grown or spread during therapy or observation. Other terms used to describe disease progression are relapse, treatment resistance, or resistant disease.
Primary or Frontline Therapy	This term is used to describe the first therapy that a patient receives. The choice of primary therapy depends on the type of lymphoma and the characteristics of the disease.
Refractory Disease	This term is used to describe lymphoma that does not respond to treatment or in which the response to treatment does not last very long.
Relapse	This term refers to disease that reappears or grows again after a period of remission.

Chapter 7: Treatment of Patients with Lymphoma

This chapter overviews the most common therapies currently used in the treatment of lymphoma. It is important to note that each type of lymphoma is different, and a treatment that works for one type may not necessarily be the best treatment choice for another type. For detailed descriptions of the treatments approved for each type of lymphoma, see Chapter 11 in Part 2 and Chapter 14 in Part 3 of this guide.

Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was published. Read Chapters 12 and 15 to learn more about emerging treatments under investigation.

How are Drugs Given?

Depending on the regimen, patients may receive their drug treatments *orally* (as a pill or capsule that is swallowed), *subcutaneously* (as an injection just below the skin), *intramuscularly* (as an injection into the muscle [IM]), *intravenously* (as a liquid that is infused directly into a vein, commonly known as an "IV"), or *intrathecally* (as an injection into the fluid around the spinal cord [lumbar puncture]).

Most chemotherapy and monoclonal antibody drugs used to treat lymphoma are given by IV infusion. One main reason for this is that IVs provide flexibility in dosing, allowing the medication to be given all at once or slowly over many hours or days. Many chemotherapy drugs also cannot be given orally because they are not stable when turned into oral pills, they are not easily absorbed from the stomach and intestines into the bloodstream, or because they are too harsh for the stomach lining to tolerate. For some drugs, subcutaneous administration is possible, takes less time than IV methods, and avoids the need for a catheter (discussed below).

To administer IV drug therapy, a doctor, nurse, or physician assistant first inserts an IV catheter, which is a small flexible tube used to deliver medications into a vein. While some catheters are designed for short-term use, others can stay in the patient's body for weeks or months, making

it easier to administer multiple cycles of drug therapy over time. Several commonly used types of catheters are described in Table 7.1. Patients and caregivers should discuss with their doctor which catheter, if any, would be best for their particular situation.

Table 7.1. Catheters Used to Administer Drug Therapy

Type of Catheter	Description	Advantages	Disadvantages
Peripheral Venous Catheter	A needle is used to insert a small, flexible tube into a small vein in the hand or arm.	Can be inserted quickly and easily by a nurse; no need for surgical insertion (the catheter is inserted into the body through a surgical opening). Good for a single infusion or other temporary use.	Cannot be left in place for more than three days at a time due to infection risk. Sterile dressing (clean pads or gauzes free of bacteria used to treat wound sites) needs to be kept clean and dry and replaced daily; the line needs to be injected periodically with a blood thinner (heparin) to prevent blockage. Cannot be used to draw blood for blood tests.
Peripherally Inserted Central Catheter (PICC line)	A long, thin plastic tube is inserted into a large vein in the arm, and the tip is guided up through the body into the large vein that enters the heart.	Can be kept in place longer than a peripheral venous catheter. Can be used to draw blood sample as well as to give drugs. Good for patients who need to have many short infusions or continuous infusions in a hospital or at home.	Not intended to remain in place as long as some surgically placed catheter types. Patients must learn to clean and take care of the external tubes to prevent infection and blockage. The tubes on the outside of the body make it more obvious that a catheter is in place.

Type of Catheter	Description	Advantages	Disadvantages
Tunneled Catheter (e.g. Hickman, Broviac)	One to three tubes are surgically inserted into the subclavian vein (underneath the collarbone). Six to 12 inches of tubing remain outside the skin in the upper chest wall.	Can be left in place for months or years with low infection risk. Easy to draw blood and give drugs using standard needles without having to pierce the skin each time.	Requires a small surgery to be inserted. Patients must learn to clean and take care of the external tubes to prevent infection and blockage. The tubes on the outside of the body make it more obvious that a catheter is in place.
Infusaport or Portacath	A catheter is surgically inserted through the subclavian vein (deep vein that moves blood back to the heart) and attached to a small reservoir (port) that lies under the skin. Nothing is visible on the outside except for a bump on the chest.	Patients do not have to do anything to care for it; a nurse keeps the line open by "flushing" it once a month with a small amount of injected liquid.	Requires surgery to be inserted. Patients must be injected through the skin covering the port with a special needle each time it is used. Can be hard to use to draw blood samples because blood clots often cause clogging. Requires another minor surgical procedure to be removed.

What Types of Treatments Can Be Used in Patients with Lymphoma?

There are four general types of approaches and treatments for patients with lymphoma:

- *Active surveillance*, also known as *watchful waiting* (observation with no treatment given), in which the patient is closely monitored to see if/when treatment should be started.

- Drug Therapy, including one or more of the following types of drugs:
  - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply).
  - Immunotherapy, which helps the body's immune system attach to the lymphoma cells (monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, immune checkpoint inhibitors, radioimmunotherapy, and immunomodulators).
  - Targeted therapies, which affect specific molecules lymphoma cells use to grow and spread.
- Cellular therapy, which uses healthy human cells to replace or repair damaged tissues and/or cells:
  - Stem cell transplantation, which adds new stem cells back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells.
  - Chimeric antigen receptor (CAR) T-cell therapy, which uses the patient's own T-cells to treat cancer.
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells.

Each of these types of therapies is described below.

What is Active Surveillance?

With the active surveillance approach, patients' health and disease are monitored through regular checkups and periodic evaluation procedures, such as laboratory and imaging tests, but they do not receive any anti-lymphoma treatments. This approach is used in patients with *indolent* (slow growing) lymphomas who have no significant symptoms and would not yet benefit from treatment. Patients with non-aggressive disease continue to remain untreated if they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or of significant concern. This approach may be used after the initial diagnosis of lymphoma, after *relapse* (disease returns after treatment), or for advanced lymphoma without indication for treatment, depending on the

situation. Patients are moved from active surveillance to treatment if they begin to develop lymphoma-related symptoms or if there are signs that the disease is clearly progressing. Before initiating treatment, a biopsy is always performed to confirm that the lymphoma is not transforming into an aggressive type of NHL.

As there are a number of reasons that your team may recommend initiation of treatment, it is important to report any new or ongoing symptoms or other medical concerns during follow-up visits with your oncology team. Throughout the observation period, biopsies could be performed when there are worrisome symptoms.

Although active surveillance may not be what a patient is expecting after the diagnosis of a lymphoma, many patients can safely delay initiation of treatment for 10 years or longer (some will never need treatment). As a result, it is important to discuss with your physicians what concerns you may have related to active surveillance so that these can be addressed.

Active surveillance most often is not a treatment option for patients with *aggressive* (fast-growing) NHL or HL. Usually, treatment for these patients should start as soon as possible after diagnosis. Active surveillance is common for patients with FL, MZL, and CLL/SLL or other indolent lymphomas, who do not show signs of active disease.

PATIENT TIP

Questions to Ask Before Starting Active Surveillance

- What happens if I choose active surveillance and then change my mind?
- Will choosing active surveillance affect my prognosis?
- Will the disease be harder to treat later?
- How often will I have checkups and tests?
- Between checkups, what symptoms and other problems should I report?
- What changes will indicate that I should start active treatment?

What is Chemotherapy?

Chemotherapy drugs work by attacking lymphoma cells that may grow and multiply very quickly, which is a common characteristic of cancer cells. During chemotherapy, patients receive the treatment at certain intervals (periods), such as once every two, three, or four weeks, followed by a rest period. This regular treatment schedule is called a *cycle*. The length of the rest period and the number of cycles vary depending on the patient's disease and the types of drugs used.

Most patients with lymphoma who are treated with chemotherapy receive combination chemotherapy, meaning two or more drugs, instead of a single drug. The purpose of combining drugs is to increase how effectively they damage or kill cancer cells, to diminish the chances of the cancer cells becoming resistant to treatment, and to allow lower doses of each drug to be used to minimize side effects. The chemotherapy drugs are combined to create a *treatment regimen*—a specific schedule that determines which drugs are given on which days of each treatment cycle.

Oncology nurses are usually responsible for administering (giving) the chemotherapy prescribed. Most patients receive their chemotherapy treatments in an infusion center located in an outpatient (a patient who attends treatment at the clinic but does not stay overnight) clinic, hospital outpatient department, or doctor's office, but sometimes patients have to stay overnight in the hospital for their treatment.

Common chemotherapy regimens used for HL, NHL, are described in Chapters 14 (Table 14.1), and 11 (Table 11.1). While chemotherapy plays a very limited role in the treatment of CLL/SLL, it may be used in combination with other types of drugs (see Chapter 11, page 105 in Part 2 of this guide).

What is Immunotherapy?

The term *immunotherapy* refers to treatments that help boost the body's own immune response. The immune system normally patrols the body for cancer cells, and when a cancer cell is detected, the immune system launches an attack to eliminate it. However, some cancer cells can "hide" from the immune system and can continue to grow in an uncontrolled manner until they form tumors or spread through the body.

Immunotherapies help the immune system recognize lymphoma cells and eliminate them from the body.

For more information, read the sections below about types of immunotherapy and see the *Immunotherapy and other Targeted Therapies* fact sheet on LRF's website at lymphoma.org/publications.

What are Monoclonal Antibodies?

Plasma cells are specialized B lymphocytes that make proteins called *antibodies*. Antibodies help fight infection by recognizing and sticking to viruses, bacteria, or other foreign substances in the body. Each antibody is naturally designed to recognize one specific *antigen* (protein on the surface of certain cells).

Monoclonal antibodies are molecules that have been engineered (modified) in a laboratory to attach to one specific target (antigen) on the surface of cancer cells and they are effective for patients with cancer cells expressing that specific antigen. These antibodies are all made from one "mother" B lymphocyte, which is why they are called *monoclonal* (one clone). Once administered to the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have antigens they recognize. This can either stop or slow down the growth of cancer cells that have that specific target, or it can trigger an "alarm" that makes it easier for other cells in the immune system to recognize and destroy the cancer cell. Before beginning monoclonal antibody therapy, patients are tested for a hepatitis infection (inflammation of the liver due to infection with hepatitis virus) which could become activated.

The monoclonal antibody therapies used in lymphoma treatment are given to patients as IV infusions or subcutaneously at a doctor's office or clinic. To prevent serious allergic reactions (life-threatening immune responses to a substance that is harmless in most people) to the infusion/injection, patients are given an antihistamine such as diphenhydramine (Benadryl), acetaminophen (Tylenol), and sometimes steroids before the antibody infusion/injection. Occasionally patients will experience an allergic reaction despite the pre-medications. Your treatment team will be prepared for this and will be able to control the allergic reaction in most cases and then continue the antibody therapy.

What are Bispecific Antibodies?

A bispecific antibody is an antibody that recognizes two different antigens, which can be on the same cell (a cancer cell) or two different cells (a cancer cell and a healthy immune cell). Bispecific antibodies used to treat lymphoma are called T-cell engagers and work by linking cancer cells to healthy immune cells. Like monoclonal antibodies, bispecific antibodies can be administered through an IV or subcutaneously.

What are Antibody-Drug Conjugates?

An antibody-drug conjugate (ADC) is a chemotherapy drug attached to a monoclonal antibody. The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by damaging its DNA and/or blocking its ability to multiply. Similar to monoclonal antibodies, antibody-drug conjugates are given intravenously.

What are Immune Checkpoint Inhibitors?

Immune checkpoint inhibitors are monoclonal antibodies that recognize immune checkpoint proteins. Checkpoint proteins (such as CTLA-4/B7-1/B7-2 and PD-1/PD-L1) regulate (activate or slow down) the immune responses against the body's own cells. Some cancers can activate checkpoint proteins and thus escape being found and killed by the immune system. Checkpoint inhibitors block this mechanism, thereby restoring the immune system's ability to attack the cancer cells and rid them from the body. These drugs are given intravenously.

What is Radioimmunotherapy?

Radioimmunotherapy consists of a targeted antibody attached to a radioisotope (a particle that emits radiation). These drugs act as a "guided missile" to destroy lymphoma cells by attaching to them and delivering small doses of radiation.

What are Immunomodulators?

Immunomodulatory drugs have many ways of working against cancer cells. They cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate (activate) the immune system to help destroy cancer cells.

What are Targeted Therapies?

Targeted therapies are drugs that block molecules that cancer cells use to survive, grow and spread. By doing that, these drugs may kill the cancer cells, slow down or stop their growth, or stimulate the immune system to attack and kill cancer cells. Targeted therapies attack lymphoma cells in a more specific way than chemotherapy drugs. Common targeted therapies include:

- Kinase inhibitors, like tyrosin kinase (TK), Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3 kinase (PI3K) inhibitors.
- Histone deacetylase (HDAC) inhibitors.
- Proteasome inhibitors.
- B-cell lymphoma-2 (BCL2) inhibitors.
- Enhancer of zeste homolog 2 (EZH2) inhibitors.
- Nuclear export receptor exportin 1 (XPO) inhibitors.
- Retinoid X receptor (RXR) activators.

What is Cellular Therapy?

Cellular therapy is the introduction of *autologous* (patient's own cells) or *allogeneic* (cells from a related or unrelated donor) healthy human cells into the patient's body for medical purposes. Both stem cell transplantation and chimeric antigen receptor (CAR) T are forms of cellular therapy, and many of the steps in the procedures are similar. Stem cell transplants use unmodified (original and unchanged) autologous or allogeneic stem cells. The cells used in CAR T-cell therapy are genetically reprogrammed (the DNA of the cells is modified) in the laboratory so they can recognize and fight cancer once they have been infused back into the patient. Currently approved CAR T-cell therapies are exclusively autologous, but approaches using allogeneic cells are under investigation.

What is CAR T Therapy?

CAR T-cell therapy is a type of personalized cellular immunotherapy in which a patient's T-cells are enhanced by the addition of an engineered gene. First, the patient's blood is collected, the T-cells are separated out, and the rest of the blood is returned to the patient. The T-cells are genetically modified to produce special receptors (proteins located

inside or outside the cell that receive signals from other cells or their environment) on their surface called *chimeric antigen receptors* (CARs), which allow them to recognize and kill malignant cells. Once the CARs are genetically engineered into the patient's T-cells and grown in the lab, the patient receives chemotherapy to reduce the number of immune cells in the body and allow the CARs to work. Finally, the patient receives the CAR T-cell therapy via IV infusion typically in an inpatient hospital admission. This process can take up to 2 to 4 weeks or longer from collection to cell infusion depending on the treatment and the insurance coverage. During this period, bridging therapies (such as chemotherapy or targeted therapies) can be used to control disease while waiting for CAR-T cell therapy and reduce the risk of CAR T-cell associated toxicities.

Once in the body, the genetically modified cells can grow to large numbers and increase the immune response by directly attacking the cancer cells. The CAR T-cells can survive for long periods of time and can multiply rapidly and increase in number if they detect cancer cells. This provides ongoing tumor control and protection against recurrence. Some patients have had very good responses to CAR T-cell therapy, with no tumor cells detected after treatment.

For additional information about the process of CAR T-cell therapy, please view the *Cellular Therapy* guide on LRF's website at lymphoma.org/publications.

PATIENT TIP

Questions to Ask Before Deciding to Undergo CAR T-Cell Therapy

- Would CAR T-cell therapy be a good treatment option for me?
- Are there any medical conditions that would exclude me from getting CAR T-cell therapy?
- What are the benefits and risks associated with this procedure?
- What complications may arise as a result of receiving CAR T-cell therapy?
- What are the short- and long-term side effects I might experience?

Questions to Ask Before Deciding to Undergo CAR T-Cell Therapy *(continued)*

- What can be done to lessen side effects?
- Would choosing this treatment prevent me from getting a different kind of treatment at a later point?
- How do I identify a certified treatment center?
- How long will I need to be in the treatment center?
- How long will I need someone to care for me after treatment?
- What are the responsibilities of a caregiver?
- Will my insurance cover this procedure?
- How sick will this treatment make me?
- How will we know if the treatment is working?
- How and for how long will the treatment affect my normal activities (e.g. work, school, childcare, driving, sexual activity and exercise?)
- What is my chance of full recovery?

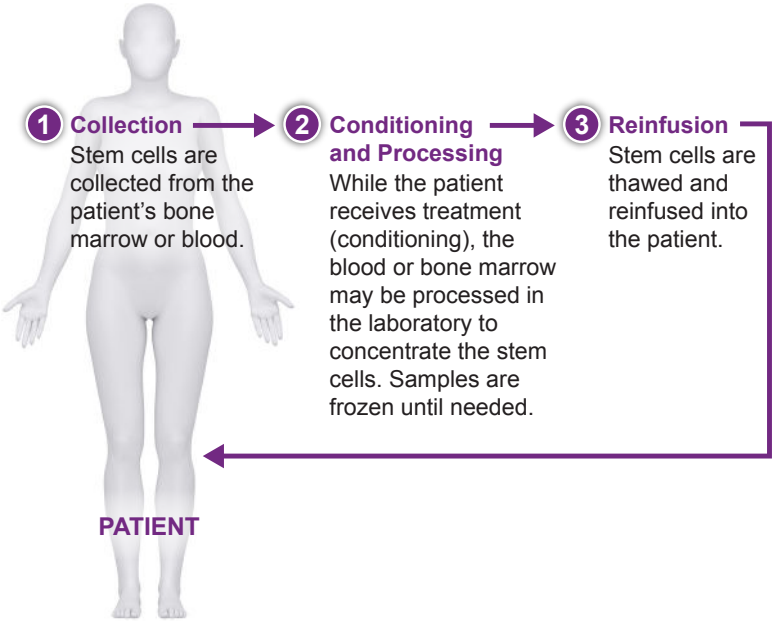
What is Stem Cell Transplantation?

A stem cell transplant adds stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells.

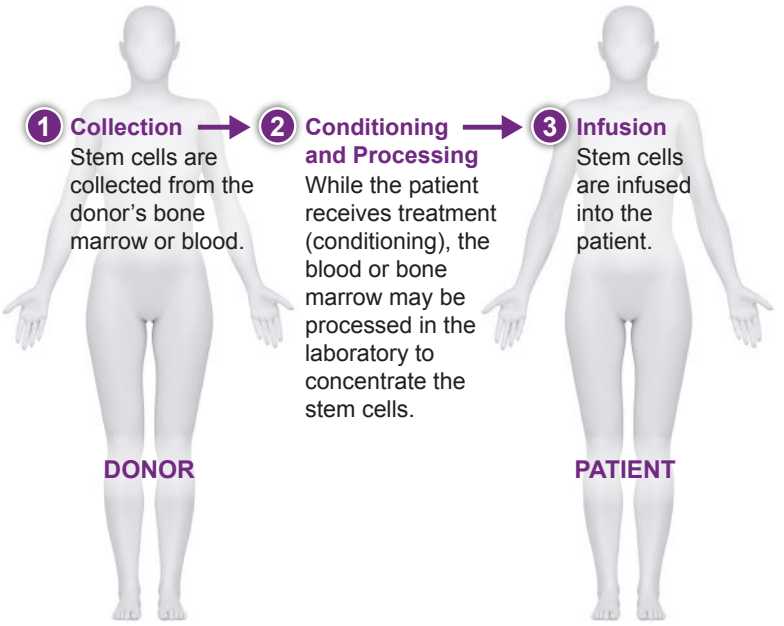
There are three types of stem cell transplantation that differ based on the source of the stem cells: *autologous*, *allogeneic* and *syngeneic*.

In an autologous stem cell transplant, patients are their own donor. Autologous stem cell transplantation is used in patients with cancers that are responding to chemotherapy. In an allogeneic stem cell transplant, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood. In a syngeneic stem cell transplant, the donor is the patient's identical twin.

AUTOLOGOUS STEM CELL COLLECTION



ALLOGENEIC STEM CELL COLLECTION



The ability to transplant the patient's own stem cells (autologous stem cell transplant) allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success.

Allogeneic transplants require immunosuppressant therapy to reduce the risk of rejection of the transplanted cells (also called 'graft') and graft-vs-host disease (GVHD, where the graft attacks the patient's healthy cells). In allogeneic, the donated cells recognize the patient's lymphoma cells as foreign and attack them, resulting in an immunologic response called the graft- versus-lymphoma (GVL) effect. For this reason, allogeneic transplantation generally controls lymphoma better than autologous transplantation. However, the toxicity and risk of complications is also higher in an allogeneic transplant, because the donor cells can recognize the normal organs of the patient as foreign and attack them, resulting in a serious complication known as GVHD. The decision about which treatment to use is a complex one and should involve a detailed discussion with the patient's doctor and a referral to a major cancer center with expertise in transplantation.

Because high-dose chemotherapy and stem cell transplantation place great strain on a patient's body, these types of therapies are not options for everyone. For patients who are not candidates for traditional stem cell transplantation, reduced-intensity transplantation (also called nonmyeloablative or mini-allogeneic stem cell transplantation) may be an option. This approach uses lower doses of chemotherapy and/or radiation prior to allogeneic transplantation. This option is available only for allogeneic transplantation, because it takes advantage of the GVL effect, in which the transplanted cells recognize the cancerous cells in the patient's body as foreign and destroy them. Patients receiving reduced-intensity transplants may avoid some of the side effects that occur with higher-dose chemotherapy. However, they are still at risk for serious side effects including GVHD, in which the donor immune cells attack the normal organs of the patient.

In deciding if transplantation is a good option, doctors consider the patient's subtype of lymphoma, health status, age, medical history, cancer stage, and response to previous therapy. For more information on stem cell transplants, view the Understanding Cellular Therapy guide on LRF's website at www.lymphoma.org/publications.

Suggested questions for patients to ask their healthcare team before deciding to undergo stem cell transplantation are listed below.

PATIENT TIP

Questions to Ask Before Deciding to Undergo Stem Cell Transplant

- What type of transplant is most appropriate for me (autologous or allogeneic) and why?
- If an allogeneic transplant is being considered, how will a donor be found? What are the risks associated with this procedure?
- What are the benefits associated with this procedure?
- What are the short-term and long-term side effects I might experience after my transplant?
- What can be done to lessen the side effects?
- Will getting a transplant make me ineligible for other lymphoma treatments or clinical trials?
- How long will I need to be in the hospital?
- Will I need someone to care for me after the transplant? For how long?
- Will my insurance cover this procedure?
- How will we know if the treatment is working?
- How and for how long will the treatment affect my normal activities (e.g., work, school, childcare, driving, sexual activity, and exercise)?
- What is my chance of making a full recovery?
- Is the transplant and related treatment part of a clinical trial? (see Chapter 8 for additional details on clinical trials).

What is Radiation Therapy?

Radiation therapy (also called *radiotherapy*) uses high-energy X-rays or other types of radiation to kill cancer cells and shrink tumors. The term is generally used to describe *external-beam radiotherapy,* in which a radiation beam is delivered from a machine to the tumor site. Radiation enters the cancer cells and damages its DNA which causes cell death.

Certain drugs can also deliver particles with radiation directly to tumor cells with little effect on the rest of the body (see the section “What is Radioimmunotherapy?” on page 56).

A radiation oncologist directs the radiation therapy. The part of the body selected to receive the radiation is called the *radiation field*. Doctors usually limit the radiation field to the affected lymph nodes, the areas immediately surrounding lymph nodes, or other areas where lymphoma is present. Doctors determine the type of radiation used and the size of the radiation field depending on the type of lymphoma and how much it has spread.

To prepare for radiation therapy, the healthcare team marks the patient’s body with tiny ink dots to make sure that only the targeted areas receive radiation. On the day of treatment, lead shields (lead barriers that protect from radiation) are used to protect the normal tissues around the radiation field. The radiation team also uses plastic forms, pillows, and rolled blankets to make patients comfortable and keep them in the proper position.

Patients lie still on a table beneath a large machine that delivers the radiation painlessly. Once the preparations have been made, it takes only a few minutes to deliver the prescribed dose. The total dose of radiation is usually divided and given over one to six weeks. During and after radiation treatment, patients need to carefully protect the radiation site from exposure to sunlight. It is most important to not become sunburned.

Some of the more common types of radiation therapy and delivery methods used for lymphoma are shown in Table 7.2.

Table 7.2. Methods for Delivering Radiation Therapy

Image-Guided Radiation Therapy (IGRT)/ Tomotherapy	■ Repeated imaging scans (CT, MRI, or PET) are used to track changes in tumor size and location throughout the course of treatment. ■ Adjustments in dose and position can be made to accommodate changes in the tumor, which can increase the accuracy of treatment and reduce the area that is exposed to radiation, saving more normal, healthy tissue.
Three-Dimensional Conformal Radiation Therapy (3D-CRT)	■ Very sophisticated computer software and advanced machines deliver radiation to a precisely shaped area of the body.
Electron Beam Radiation	■ A machine sends *electrons* (negatively-charged particles) directly to the area where the lymphoma was found and sometimes to nearby lymph nodes.
Proton Therapy	■ A charged particle called a proton is delivered in an external beam. ■ Radiation exposure to normal surrounding tissues can be reduced, which allows higher doses to be delivered to the tumor. ■ Useful therapy for patients with tumors near the heart, lungs, or esophagus that are difficult to treat with other radiotherapy methods.
Total Skin Electron Beam Therapy (TSBT)	■ A weak radiation beam that only penetrates the outer layers of the skin is directed to the entire surface of the body.
Photopheresis or Extracorporeal Photochemotherapy	■ A fraction of the patient's blood is removed from the body, treated with a chemical that makes lymphocytes more likely to die when exposed to ultraviolet radiation, and infused back into the patient.

PATIENT TIP

Questions to Ask Before Starting Radiation Therapy

- What is the goal of my radiation therapy?
- How will the radiation be given?
- How long will the treatment last, and how often will it be given?
- How will I feel during the therapy?
- What are the side effects of radiation therapy? Is there anything that can be done to prevent them?
- Are there any lasting side effects?
- What can I do to take care of myself during and after the therapy?
- How will we know if the radiation therapy is working?
- How will the radiation treatment affect my normal activities (work, school, childcare, driving, sexual activity, and exercise)?

What is Palliative Radiation?

Radiation may be given to help ease symptoms caused by the spread of tumors in the body. This type of therapy is called *palliative radiation*. Growing tumors can press on organs and nerves, causing pain and inhibiting function. In this case, the goal of radiation treatment is to ease pain and improve the quality of life of the patient, not to cure the lymphoma or increase survival time. Palliative radiation is frequently combined with anti-inflammatory (agents that treat inflammation) and pain medications to maximize relief.

What is Maintenance Therapy?

Maintenance therapy refers to the ongoing treatment of patients whose disease has responded well to treatment. The purpose of maintenance therapy is to enhance (improve) response to prior therapy and to improve the duration (period) of remission.

Maintenance therapy in most situations consists of drugs given at the same doses during longer intervals than those used during initial therapy. Depending on the type of lymphoma and the drugs used, maintenance therapy may last for weeks, months, or even years.

For more information on maintenance therapy, see the Maintenance Therapy fact sheet on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org/publications.

PATIENT TIP

Questions to Ask About Maintenance Therapy

- Is maintenance therapy an option for me?
- Why are you recommending maintenance therapy?
- Why are you NOT recommending maintenance for me?
- What are the benefits and risks?
- What are the long-term side effects of maintenance therapy?
- Am I at a higher risk for infections by being on maintenance therapy?
- How often and for how long will I receive this treatment?
- Does my insurance cover this treatment?
- Is this better for me than active surveillance?

What are Complementary and Alternative Therapies?

Complementary therapy can be used in addition to standard therapy to help improve a patient's quality of life and to relieve the effects of drug therapy, radiation, and surgery. Motivations for using complementary therapy include improved physical and emotional well-being. **Patients and caregivers should talk to their doctor and healthcare team before starting any form of complementary therapy, because a few of these approaches may interfere with their lymphoma treatment and make it less effective.** A healthy lifestyle that includes regular exercise may improve overall quality of life. Herbal therapies (the use of plants to treat disease), supplements, vitamins, and other oral agents (agents taken

by mouth), however, may cause side effects, have drug interactions (a reaction between the supplement and the treatment drug), or make their lymphoma treatment less effective. Marketing may suggest that a product is "natural" or that it is an "anti-cancer therapy" however, it is important to discuss this with the healthcare team to ensure the product is safe and compatible with the prescribed treatment plan. Open communication is essential to ensure safe, effective, and comprehensive care throughout treatment and following treatment as a cancer survivor. Table 7.3 outlines some forms of complementary therapy for cancer, also known as integrative medicine or integrative oncology.

Table 7.3. Forms of Complementary Therapy

Acupuncture	■ Uses ultra-thin needles applied to specific points on the body. The process is safe and painless, and the needles are disposed of after one use. ■ May relieve pain, nausea, fatigue, hot flashes, and *peripheral neuropathy* (numbness and pain in the hands and feet) associated with some treatments. ■ May also help decrease mild depression and other symptoms and side effects.
Chiropractic and Massage Therapy	■ Most commonly used modalities (methods) can help relieve side effects and stress. ■ A special type of massage called *oncology massage* is designed specifically for patients with cancer to help manage stress, pain, swelling, and other side effects without causing harm or interfering with cancer treatments. ■ Performed by a massage therapist who is certified in oncology massage. ■ Massage does not cause the lymphoma to spread.
Herbal Therapy	■ Talk with your doctor before using herbal therapies. Some herbal therapies, such as St. John's wort, may interfere with cancer medications.
Mind/Body Therapies	■ Examples of mind/body therapies include meditation, guided imagery, self-hypnosis, Tai Chi, and yoga. ■ Meditation, guided imagery, and self-hypnosis can help manage stress. ■ Yoga and Tai Chi have been shown to minimize stress and improve balance and flexibility.

Alternative therapy refers to any treatment used instead of standard therapy (accepted by medical experts as the proper treatment for a specific disease and used widely by healthcare professionals). Alternative therapies are not recognized as effective by the medical profession. **Currently, there are no proven alternative therapies to conventional cancer care for patients with lymphoma. Patients should not use alternative remedies to replace the care suggested by their doctors.**

For more information about complementary therapies, please view the Integrative Oncology factsheet on LRF's website at lymphoma.org/publications.

Chapter 8: Clinical Trials

What Is a Clinical Trial?

A clinical trial is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. The investigators (responsible for planning, conducting, and reporting results in a study) in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial. Strict rules and oversight (supervision) procedures make sure that clinical trials are designed and run in a way that protects the rights and safety of the people who volunteer to participate. It can sometimes take years for a clinical trial to be completed and for the results to be compiled and published.

In the United States, a new drug must pass through a strict approval process governed by the U.S. Food and Drug Administration (FDA; organization responsible for the approval of drugs and making sure that drugs are safe and efficacious) before it can become a standard therapy for use in humans. The FDA-regulated approval process for drugs includes preclinical studies (done in laboratories) and clinical trials (done in hospitals and clinics). In addition to the FDA, all trials must be approved by an Institutional Review Board (IRB) consisting of experts (such as doctors and investigators) and lay persons (someone who is not an expert or does not have knowledge in a certain area) to ensure that the study is conducted in an appropriate and ethical (being right in the moral sense) manner that does not endanger patients in any way.

As shown in Table 8.1, there are four main types or phases of clinical trials. The first three (Phase I, Phase II, and Phase III) are usually required before a drug is considered for approval by the FDA. Certain drugs can receive a temporary approval through the FDA accelerated approval process until a phase III trial is completed. Phase IV trials, sometimes called postmarketing studies, are conducted after a drug has received FDA

approval. Each phase is designed to find out certain information, building upon the information learned from the previous phase. Patients may be eligible to participate in different types of clinical trials depending on their health status, type and stage of lymphoma, and the types of treatments, if any, they have previously received.

Table 8.1. The Four Main Phases of Clinical Trials

Phase	Purpose	Typical Number of Volunteer Patients
Phase I	■ To identify a safe dose (the quantity and strength of a drug) of a new drug or combination of drugs (which may or may not be approved). ■ To decide on a dosing schedule for the drug. ■ To see which side effects are related to therapy.	■ 6-30 patients with 1 or more types of cancer.
Phase II	■ To see if a new treatment is effective against a certain type of cancer at the dose determined in Phase I. ■ To confirm and learn more about the side effects identified in Phase I.	■ ~100 patients with the same type of cancer. ■ More than 100 patients in 2 study arms for randomized Phase II studies.
Phase III	■ To compare the new treatment or new use of an existing treatment with the current standard treatments. ■ To obtain detailed information about how well the treatment works and the types and intensity of side effects it causes.	■ From 100 to several thousand patients with the same type of cancer. ■ Patients are randomly assigned to a treatment group (standard therapy or experimental treatment).
Phase IV	■ To find out more information about the long-term safety and efficacy of a new treatment after it has already been approved by the FDA and is being used by patients outside of a clinical trial.	■ Several hundreds to several thousand patients with the same type of cancer.

Why Is a Placebo Sometimes Used in Phase III Trials?

A *placebo*, or sugar pill, is an inactive ingredient that is used as a comparator (to be used for comparison with trial drug) in some randomized (random selection of patients or samples) clinical trials. We know from past studies that sometimes patients in a clinical trial treated with placebo experience benefits from participation. This may happen because patients enrolled in clinical trials have extra people involved in their care, may have more frequent visits, or other reasons. For these reasons and others, having a group who receives the placebo for comparison can help researchers to better understand the additional benefits of the new treatment being tested. The placebo is made to have the same appearance as the experimental pill, or to have the same appearance as the experimental IV agent, so that patients cannot tell whether they have been randomized to the control group receiving the placebo or the experimental group receiving the new treatment. In some trials known as double-blind studies, the doctors and nurses also do not know who is receiving which type of treatment.

In clinical trials for cancer therapies, patients are never given a placebo in place of an effective standard therapy. In Phase III cancer trials that use a placebo, the placebo is given in addition to, not instead of, the standard treatment regimen. Clinical trials are never conducted in a way that would deny patients an effective therapy.

When Should a Clinical Trial Be Considered?

While clinical trials can be a good option for patients lacking treatment options at all stages of disease, they are often useful for patients with relapsed (disease came back after treatment) or refractory (disease does not respond to treatment) lymphoma.

Clinical trials offer both benefits (advantages) and risks (the possibility of having a negative effect). Patients in clinical trials who are randomized to the experimental group may be able to benefit from a new treatment that is not otherwise available to all patients. However, this new treatment may or may not be more effective than the standard therapy. At the very least, patients who are randomized to the control group receive the standard therapy that they would have received if they had not enrolled in the trial.

Another advantage of clinical trials is that the health of enrolled patients is monitored very closely. The healthcare team studying the new treatment can explain all the possible benefits and risks of a specific clinical trial.

Every clinical trial is led by a principal investigator who is a medical doctor. Clinical trials also have a research team that may include doctors, nurses, physician assistants, social workers, and other healthcare professionals. Patients usually continue regular visits with their current healthcare provider, who may work with the research team to ensure that any investigational treatment does not interfere with their current medications or treatments for other medical conditions. There are several entities and processes in place that supervise clinical trials to ensure the patients' safety. These include safety monitoring boards (a team of people responsible to monitor safety), monitoring processes and audits (inspections).

Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapters 12 and 15 further describe clinical trials and some of the options currently under investigation.

What is Informed Consent in a Clinical Trial?

Informed consent is a process in which patients learn about the clinical trials they are interested in joining. During this process, members of the clinical trial research team explain:

- The purpose of the study.
- The factors used to decide if a patient is allowed to participate in the study.
- The tests, procedures, and consultations participants are expected to undergo.
- The type of treatments provided in the study.
- The possible risks, benefits, and alternatives.
- The rights of patients to decide whether or not to participate and to leave the study at any time.

The research team answers questions and provides written information about the trial. After the team explains all of the details and the patient does not have any more questions, the patient is asked to read and sign an informed consent document before entering the study that details all the trial information discussed, describes how his or her records are kept private, and confirms that the patient was given information on the potential risks and benefits and the alternatives to enrolling in the trial. In addition, the healthcare provider also signs the same document.

It is important for patients to remember that even after signing the consent form, they can leave the study at any time. If a patient leaves the study or decides not to take part in the study, the doctor can discuss other treatment options available. A list of questions patients might ask their doctor about clinical trials is provided on the following page.

What is the Cost of Participating in a Clinical Trial

Clinical trials are very expensive for the study sponsor (entity that pays for or contributes to the costs of the trial). However, the cost to the patient varies depending on the trial, who is sponsoring the trial, what portion of the trial-related expenses the sponsor has agreed to cover, and the patient's health insurance coverage. Patients should ask their doctor about the potential costs of participating in any clinical trial under consideration and what clinical trials may be most appropriate for them. Here are some additional sources of clinical trial information:

- The Lymphoma Research Foundation's Clinical Trials Information Service at (800) 500-9976 or helpline@lymphoma.org.
- The NCI's Cancer Information Center at (800) 4-CANCER or the NCI's Clinical Trials Referral Office at (888) NCI-1937.
- The NIH websites at www.cancer.gov and www.clinicaltrials.gov.
- Local cancer centers and institutions affiliated with universities.

PATIENT TIP

Questions to Ask About a Clinical Trial

- What is the purpose of this clinical trial?
- What is the current phase of this trial?
- Why are you recommending this clinical trial for me?
- Who is sponsoring this trial (the National Cancer Institute [NCI], a cancer center, an international study group, other state or national study group, or a pharmaceutical/ biotechnology company)?
- Who has reviewed and approved this clinical trial?
- Is there a screening period? How long will take to know if I am eligible to participate in the trial?
- Does this clinical trial include the additional use of a placebo (no active ingredient/no intervention)?
- Are transplants allowed in the trial?
- Is radiation allowed in the trial?
- How long will the study last? Where will it take place?
- Will I receive a drug treatment schedule? What is the schedule for doctor visits and other procedures?
- When can I start receiving therapy?
- What are the risks involved?
- What are the possible benefits? If I benefit from the intervention, will I be allowed to continue receiving it after the trial ends?
- What are my responsibilities during the clinical trial?
- What kinds of tests, procedures, or treatments will be performed? How many and how often?
- Will I be in any discomfort or pain?
- Will I be able to see my own doctor during the clinical trial?
- What type of long-term follow-up care is part of this trial?
- What costs will I be responsible for? Who will pay for my participation? Will I be reimbursed for other expenses?
- What happens if my health gets worse during the clinical trial?

Chapter 9: Hospital Admission

What Are Some Reasons That Patients May Be Admitted to the Hospital?

Hospital admission usually occurs either from the emergency room or through direct admission by the patient's doctor. In the case of a direct admission, the doctor decides that the patient needs to be admitted and calls ahead to reserve a bed for the patient. If the patient is admitted by a doctor in the emergency room, the patient's doctor is contacted and informed that the patient is in the hospital.

Treatment teams conduct daily visitation rounds to check on their patients. The nurse can tell patients when their doctor will come to see them that day. It is a good idea for family members to know when the doctor is likely to be coming so they can be there to ask questions.

Whether admitted through the emergency room or a direct admission, patients may be first evaluated by a hospitalist, resident physician or a nurse practitioner. Hospitalists are doctors employed by or consulting for the hospital. Their specialty is typically internal medicine (that covers a wide range of conditions affecting the internal organs) or in some cases for pediatric patients, they are pediatricians. Patients are also assigned a case manager (usually a nurse) who works with the patient's healthcare team.

What Should Patients Bring With Them to the Hospital?

When being admitted to the hospital, being prepared can ease the process of admission and positively impact patients' care. A brief list of items for patients to take with them is shown on the next page.

PATIENT TIP

What to Bring if You Are Being Admitted to the Hospital

- Identification (driver's license, student ID) and emergency contact information (relatives' and friends' names and phone numbers).
- List of all allergies and the reaction that occurs in response to exposure (especially important for latex and medication allergies).
- List of all current prescription medications (name, dosage, and frequency) as well as other products taken such as over-the-counter medications and vitamins (instead of making a list, you can also place all medications in a bag and bring them with you).
- List of all medical conditions other than lymphoma, such as hypertension, epilepsy, or an active ulcer.
- List of all surgeries (even elective plastic surgeries) regardless of how long ago they occurred.
- List of all physicians currently treating you.
- Copy of any completed advanced directives (a legal document that explains how you want medical decisions about you to be made if you cannot make the decisions yourself).
- All insurance cards, a checkbook, a credit card, and a minimal amount of cash.

Do not bring valuables. Leave most money and jewelry at home.

If patients have access to an up-to-date and complete medical record through a patient portal, flash drive, or phone app, they should bring the security code and the name of the website, or the flash drive, phone app, or other device that contains the health information.

What Are Patients' Rights?

Patients' rights are listed in the hospital's Patient's Bill of Rights. See the tips on the next page for more information about these rights.

PATIENT TIP

Your Rights As a Patient

- You must be given a medical screening examination and be evaluated for care whenever you are admitted to a hospital.
- You have the right to considerate and respectful care.
- You have the right to complete information regarding all aspects of your current condition.
- You have the right to know the names of all doctors and healthcare personnel providing your care.
- You have the right to sufficient information about the benefits and risks for all treatments or procedures to enable you to provide informed consent.
- You have the right to refuse any treatment.
- You have the right to privacy—no members of your healthcare team may talk about your condition or care to anyone outside of that team.
- If you must be transferred to another facility, information about why you require transfer must be provided, and the institution that you are being transferred to must have accepted responsibility for your care prior to transfer.
- You have the right to know whether the hospital has any relationship to other healthcare or educational institutions and if/ how this relationship impacts your care.
- You have the right to be informed about your continuing healthcare requirements after you are discharged.
- You have the right to examine and receive an explanation of your bill.
- You have a right to know what hospital rules and regulations apply to your conduct.
- You have the right to have a translator present if English is not your first language.

What Do Patients Need to Know About Informed Consent Documents When in the Hospital?

Patients who are admitted to a hospital may be asked to sign informed consent documents. These documents enable patients to make an educated decision about which treatments and procedures they are willing to receive. Patients should read the informed consent documents carefully and request an explanation of anything they do not completely understand. Signing these documents indicates that the patient understands and agrees to the risks and benefits of the treatments/procedures being performed. The tips below may help patients know what to look for in an informed consent document.

PATIENT TIP

What to Look for in the Hospital Informed Consent Document

- Indication of whether you are being enrolled in research.
- Alternatives to the proposed treatment.
- Names of the physician(s) performing your treatments/ procedures.
- Risks and benefits of the treatments/procedures you are agreeing to.
- An explanation of what will be done with any tissue or fluid samples removed and any photos or videos taken.

What Do Patients Need to Know at Discharge?

When the patient is ready to be discharged, make sure the case manager addresses the subjects identified in the following patient tips. Patients should receive a list of symptoms that will prompt them to contact their doctors if they develop.

PATIENT TIP

Topics for the Case Manager to Address Before Discharge

- Are there any new limitations to what you can do at work or at home? If so, your doctor can provide a note for your employer if needed.
- Will you need physical therapy?
- If you need any new medical equipment, where can it be obtained? Who will order it? Obtain a phone number to ensure you can follow up if there are any problems with equipment delivery.
- Will you need home nursing care or other arrangements? Will this be covered by insurance?
- What new medications will you need to take, and for how long?
- Does your insurance cover the new medication as an outpatient prescription? If not, or if you do not have insurance, what will the cost be?
- If you do not have insurance, does the hospital have a sliding- scale fee or charity care?
- Are there alternative medications you can take if the cost is beyond your capacity to pay?
- What are the side effects of the new medications?
- Will they interact with any medications you are currently taking?
- What symptoms might you develop? Which of those symptoms should prompt a call to your doctor?
- Are there other instructions from your doctor or the hospital physician?
- With whom should you follow up and when?
- If you are to schedule your own follow-up, whom do you call?

Itemized hospital bills should be examined carefully to make sure no mistakes were made. If there are discrepancies between the bill and the care the patient received, they should be brought to the attention of both the hospital and the insurance company