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FOR PATIENTS & CAREGIVERS

Non-Hodgkin Lymphoma



Revised 2020

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

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



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

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Introduction

This booklet provides information about non-Hodgkin lymphoma (NHL) for patients and their families. “Lymphoma” is a general term for a group of blood cancers that originate in the lymphatic system.

This booklet covers many NHL subtypes and provides detailed information about the diagnosis, staging, treatment and other aspects of the more common ones. It includes brief descriptions of normal blood, bone marrow and the lymphatic system, as well as a glossary of health terms to help readers understand information that may be new to them.

An estimated 678,222 people in the United States are either living with or in remission from NHL. About 74,200 people were expected to be diagnosed with NHL in 2019 (see *Incidence, Causes and Risk Factors* on page 46). Advances in the treatment of NHL are resulting in improved remission and cure rates. New treatment approaches are being studied in clinical trials for patients of all ages and for all disease stages.

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Lymphoma

Lymphoma is a general term for a group of blood cancers that originate in the lymphatic system, part of the body’s immune system. The two major types of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

Both HL and NHL are further classified into subtypes. Knowing the subtype of your disease is very important because the treatment approach is based on the subtype. Information about treatments for specific NHL subtypes begins on page 23.

For more information about Hodgkin lymphoma, see the free LLS booklet *Hodgkin Lymphoma*.

Non-Hodgkin Lymphoma Basics

“Non-Hodgkin lymphoma (NHL)” is the term for a diverse group of blood cancers that share a single characteristic—they all arise from lymphocytes. Lymphocytes are white blood cells that are part of the body’s immune system. There are three main types of lymphocytes: B cells, T cells and natural killer (NK) cells. In lymphoma, a lymphocyte undergoes a malignant (cancerous) change and then multiplies, eventually crowding out healthy cells and creating tumors.

These tumors generally develop in the lymph nodes or in lymphatic tissue found in organs such as the stomach, intestines or skin. In some cases, NHL involves blood and the bone marrow (the spongy tissue in the hollow, central cavity of bones, where blood cell formation occurs). Lymphoma cells may develop in just one place or in many sites in the body (see *Signs and Symptoms* on page 6).

Although some types of leukemia are closely related to NHL, leukemias and lymphomas are different. Leukemias begin when a cell undergoes a change (mutation) in the bone marrow. Lymphomas begin when a cell in a lymph node or in some other lymphatic structure undergoes a mutation. Lymphomas can develop in the skin, gastrointestinal tract, or other sites in the body. It is important to recognize that leukemias, which originate in the bone marrow, often involve lymph nodes or other organs. Similarly, lymphomas, which originate in lymphatic tissue outside the bone marrow, often involve the bone marrow.

More than 60 specific NHL subtypes have been identified and assigned names, called “diagnostic designations,” by the World Health Organization (WHO). The Revised European American Lymphoma and World Health Organization (REAL/WHO) classification of non-Hodgkin lymphoma categorizes NHL subtypes by the characteristics of the lymphoma cells, including their appearance, the presence of proteins on the surface of the cells and their genetic features. The prognosis and treatment approach for different NHL subtypes are influenced by findings from studying the diseased cells and tissues under a microscope, so biopsy samples should be examined by a hematopathologist (a doctor who specializes in the diagnosis of blood disorders and blood cancers).

One way that NHL subtypes are classified is by cell type. Some NHL subtypes, such as diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), involve lymphocytes called “B cells.” Other subtypes, such as peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL), involve lymphocytes called “T cells” or “natural killer (NK) cells.”

Specialists further classify the NHL subtypes according to the rate of disease progression, either fast growing (aggressive) or slow growing (indolent). Aggressive lymphoma subtypes (also called “high-grade NHL”) account for about 60 percent of all NHL cases. Diffuse large B-cell lymphoma is the most common aggressive NHL subtype. Slow-growing (indolent) subtypes account for about

40 percent of all NHL cases. Follicular lymphoma is the most common subtype of indolent NHLs. When indolent lymphomas are first diagnosed, patients have fewer signs and symptoms than patients with aggressive lymphoma subtypes. Whether the diagnosed subtype is aggressive or indolent determines the appropriate treatment, so getting an accurate diagnosis is very important. In some cases, indolent forms of NHL later transform into an aggressive form of the disease.

Table 1, below provides a list of some of the diagnostic designations for NHL subtypes based on the WHO classification, categorized by cell type (B cell, T cell or NK cell) and rate of progression (aggressive or indolent). The percentages listed reflect the frequency of diagnosed cases of the most common NHL subtypes.

Table 1. Diagnostic Designations for Non-Hodgkin Lymphoma (NHL)

Mature B-cell lymphomas (about 85%-90% of NHL cases)

Aggressive

- Diffuse large B-cell lymphoma (DLBCL) (31%)
- Mantle cell lymphoma (MCL) (can present as aggressive or indolent) (6%)
- Lymphoblastic lymphoma (2%)
- Burkitt lymphoma (BL) (2%)
- Primary mediastinal (thymic) large B-cell lymphoma (PMBCL) (2%)
- Transformed follicular and transformed mucosa-associated lymphoid tissue (MALT) lymphomas
- High-grade B-cell lymphoma with double or triple hits (HBL)
- Primary cutaneous DLBCL, leg type
- Primary DLBCL of the central nervous system
- Primary central nervous system (CNS) lymphoma
- Acquired immunodeficiency syndrome (AIDS)-associated lymphoma

Indolent

- Follicular lymphoma (FL) (22%)
- Marginal zone lymphoma (MZL) (8%)
- Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL) (6%)
- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (5%)
- Lymphoplasmacytic lymphoma (1%)
- Waldenström macroglobulinemia (WM)
- Nodal marginal zone lymphoma (NMZL) (1%)
- Splenic marginal zone lymphoma (SMZL)

Table 1. (cont.)

Mature T-cell and natural killer (NK)-cell lymphomas (about 10%-15% of NHL cases)

Aggressive

- Peripheral T-cell lymphoma (PTCL), not otherwise specified (6%)
- Systemic anaplastic large-cell lymphoma (ALCL) (2%)
- Lymphoblastic lymphoma (2%)
- Hepatosplenic gamma/delta T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
- Enteropathy-type intestinal T-cell lymphoma
- Primary cutaneous anaplastic large-cell lymphoma

Indolent

- Cutaneous T-cell lymphoma (CTCL) (4%)
- Mycosis fungoides (MF)
- Sézary syndrome (SS)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma (ENK/TCL), nasal type

This table is based on information presented in *The 2016 revision of the World Health Organization classification of lymphoid neoplasms*. The descriptive parts of the names (eg, follicular, mantle cell or marginal zone) of some disease subtypes refer to the specific areas of normal lymph nodes where the lymphoma originated.

Sources: Armitage JO, Weisenberger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. *Journal of Clinical Oncology*. 1998;16(8):2780-2795. doi:10.1200/JCO.1998.16.8.2780

You will have many concerns, questions and considerations when you are diagnosed with non-Hodgkin lymphoma. Before treatment begins, ask your doctor and other members of your healthcare team any questions you have about treatment planning and related issues, such as the possible long-term and late effects of treatment, including effects on fertility. Be sure you understand the doctor's responses and discuss any concerns or issues that arise.

Signs and Symptoms

A person who has signs or symptoms that suggest the possibility of non-Hodgkin lymphoma (NHL) is usually referred to a blood cancer specialist called a “hematologist-oncologist.” This doctor will order additional tests and a tissue biopsy to make a diagnosis (see *Diagnosis* on page 8). Since the signs and symptoms of NHL are also associated with a number of other, less serious diseases, these test results can also be used to rule out a diagnosis of NHL.

There are about 600 lymph nodes in the body. The most common early sign of NHL is painless swelling of one or more lymph node(s). For example,

- Most patients with NHL have one or more enlarged lymph node(s) in the neck, armpit or groin (see **Figure 1** on page 7).
- In fewer patients, a swollen node appears near the ears, the elbow or in the throat near the tonsils.

Occasionally, the disease starts in a site other than in a lymph node, such as a bone, a lung, the gastrointestinal tract or the skin. In these circumstances, patients may experience symptoms that are associated with that specific site.

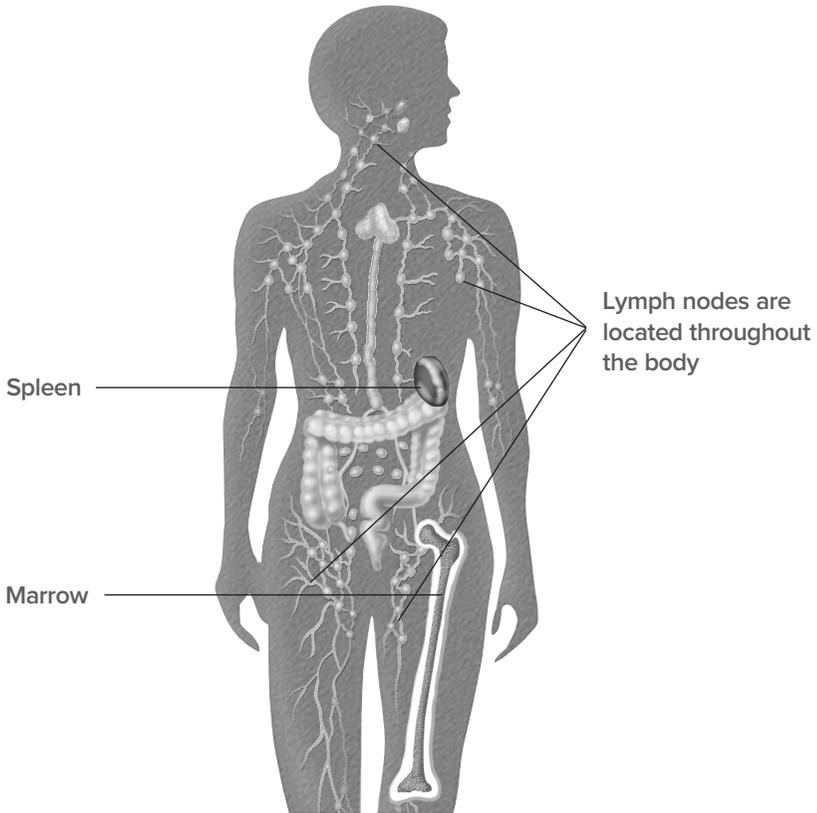
Common Signs and Symptoms. These include

- Painless swelling in one or more lymph node(s)
- Unexplained fever
- Drenching night sweats
- Persistent fatigue
- Loss of appetite
- Unexplained weight loss
- Cough or chest pain
- Abdominal pain
- Sensation of bloating or fullness (due to an enlarged spleen)
- Itchy skin
- Enlargement of the spleen or liver
- Rashes or skin lumps.

Some people have no signs or symptoms, and so the disease may be discovered during a routine medical examination or while the patient is under care for an unrelated condition.

B Symptoms. The term “B symptoms” is used to refer to fever, drenching night sweats and loss of more than 10 percent of body weight over 6 months. B symptoms are significant to the prognosis and staging of the disease. Other NHL symptoms, such as itching and fatigue, do not have the same prognostic importance as B symptoms and are not considered to be B symptoms.

Figure 1. Non-Hodgkin Lymphoma (NHL) and the Lymphatic System



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

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

Diagnosis

An accurate diagnosis includes determination of the specific subtype of non-Hodgkin lymphoma (NHL), and is one of the most important aspects of a person's care. A precise diagnosis will help the doctor to

- Estimate the rate of disease progression
- Determine the appropriate treatment.

A diagnosis of NHL is usually made based on microscopic examination of a lymph node biopsy specimen (a piece or "sample" of lymph node obtained from a biopsy procedure). It is important to receive an accurate diagnosis and to know the NHL subtype. Patients may want to ask the doctor to write down the diagnosis for them, including the specific subtype.

Physical Evaluation. The doctor will take a comprehensive medical history and ask questions regarding either the absence or presence of B symptoms. Physical examination will include measurement of all accessible lymph node groups, as well as the size of organs such as the spleen and liver.

Lymph Node Biopsy. Making an accurate diagnosis of the patient's specific subtype of NHL can be challenging. It requires an experienced hematopathologist (a doctor who specializes in diagnosing diseases of the blood and marrow) to prepare the tissue samples from a biopsy, the procedure used to obtain a sample of lymph node tissue. Then the hematopathologist examines the tissue under the microscope and analyzes the findings. If there is any doubt about the diagnosis, or to confirm it (in the case of a rarer type of lymphoma, for instance), it may be necessary to get a second opinion from another hematopathologist.

A biopsy of an involved lymph node or other tumor site is needed to confirm the NHL diagnosis and subtype. A type of needle biopsy called fine-needle aspiration (FNA) may be done, but the lymph node tissue sample that can be obtained through a needle is usually not sufficient for the hematopathologist to make a conclusive diagnosis. To ensure that there is enough tissue for the hematopathologist to make an accurate diagnosis, either a small area of tissue is taken (an incisional biopsy) or an entire lymph node is removed (an excisional biopsy). The decision about which type of biopsy to use is based on the location of the tumor. Tissue is generally removed after the patient is given a local anesthetic.

The tissue sample is placed on a slide, along with a preservative, and then stained with dyes. Next, the slide is examined under a microscope, and the doctor studies the size and shape of the cells and how they are arranged.

The examination findings may confirm that the person has lymphoma, as well as identify the type of lymphoma. Sometimes, hematopathologists can determine a person's NHL subtype by looking at the cells from the tissue sample. They will note the distinctive patterns of changed cells and use that information to identify the NHL subtype. Usually, other types of tests are also needed to confirm the diagnosis.

Non-Hodgkin lymphoma can develop in parts of the body that do not involve lymph nodes, such as a lung or bone. When lymphoma is detected exclusively outside of the lymph nodes, it is called “primary extranodal lymphoma” and the biopsy sample is taken from that involved tissue.

Additional Tests. Additional tests that may be necessary include

- Immunophenotyping—A technique used to distinguish NHL from other types of lymphoma or other cancerous or noncancerous conditions. The hematopathologist looks for the presence of certain antigens or markers on the surface of the cells in a blood or bone marrow sample in order to identify NHL cells and confirm the diagnosis. Immunophenotyping can further help determine whether the lymphoma cells are B cells, T cells or natural killer (NK) cells.
- Flow cytometry—In this technique, cells are taken from the blood or tissue biopsy sample and put in a machine that detects which proteins (also called “markers” or “antigens”) are expressed in the lymphoma cells.
- Cytogenetic analysis—This test is used to see if any chromosomal abnormalities are present in dividing cells in a blood or bone marrow sample. One of the main methods is fluorescent in situ hybridization (FISH), a laboratory test that uses special dyes to identify abnormalities in chromosomes, such as translocations and deletions. Chromosomal abnormalities are important considerations in identifying specific subtypes of NHL and choosing the most effective treatment approach.
- Gene expression profiling and microarray analysis—These tests are used to identify cancer subtypes and risk factors. The findings help doctors to predict how patients will respond to treatment, as well as which patients may be at increased risk for disease relapse. Gene expression profiling and microarray analysis are mostly used as research tools and are not generally used in clinical practice.

Staging

Doctors use findings from physical examinations, imaging and laboratory tests to evaluate the extent of the disease. The doctor needs this information to determine the “stage” of the disease (see **Table 2** and **Table 3** on pages 13 and 14 and **Figure 2** on page 15). Staging is a very important part of treatment planning.

Imaging Tests. The physical examination and imaging tests help the doctor to evaluate

- The location and distribution of lymph node enlargement
- Whether organs other than the lymph nodes are involved
- If there are very large masses of tumors in one or more site(s).

Imaging is a very important part of the staging and management of non-Hodgkin lymphoma (NHL). A doctor may first order imaging tests when a patient’s medical history and physical examination suggest a possible diagnosis of NHL. The imaging test(s) may show enlarged lymph nodes in either the chest or abdomen, or both. Tumor masses may also occur outside the lymph nodes in lung, bone or other body tissues.

The imaging tests may include

- Chest x-rays
- A computed tomography (CT) scan—A CT scan (also known as a “CAT scan”) uses special x-ray equipment to take multiple images from different angles around the body. A computer then processes the information from the images and produces a composite image that shows a cross section of the area being examined. Patients undergo CT scans of the neck, chest, abdomen and pelvis—all the areas where lymph nodes are present—to identify areas of disease. A CT scan can also show whether there is involvement of the lungs, liver and/or other organs, which is helpful staging information. A CT scan shows where the lymphoma is located and can measure the size of the mass.
- Magnetic resonance imaging (MRI)—An MRI scan is done in select cases for NHL staging. It uses a powerful magnet and radio waves linked to a computer to create clear and detailed cross-sectional images (slices) of the body. The “slices” can then be displayed on a video monitor and also saved on a disk for future analysis.
- A positron emission tomography-computed tomography (PET-CT) scan—This procedure combines the techniques of both PET (an imaging technique that produces a 3D image of functional processes in the body) and CT imaging. Both tests are done at the same time and by the same machine. In a PET scan, a small amount of a radioactive sugar called “fluorodeoxyglucose (FDG)”

is injected into the patient. It is used to show differences between healthy and unhealthy tissue. The PET scanner detects the radiation given off by the FDG and produces color-coded images of the body that show both normal and cancerous tissue.

A PET-CT scan reveals information about both the structure and function of cells and tissues in the body during a single imaging session. It provides a more detailed picture of where the cancer is located in the body than either test does by itself.

Use of PET scans is increasing, not only to stage the disease precisely, but also to determine and mark radiotherapy margins on the body (when needed), to confirm response to treatment and to provide a baseline to assess future treatment response.

Blood Tests. Blood tests are used to determine whether lymphoma cells are present in the blood; check for indicators of disease severity by examining blood protein levels; assess kidney and liver function; and measure important biological markers that are helpful prognostic indicators for several NHL subtypes.

Examples of the blood tests used to determine the extent of disease and when treatment is needed include

- A complete blood count (CBC)—This test measures different components of the blood. The results include counts of red blood cells, white blood cells and platelets. A CBC may show
 - Anemia (low numbers of red blood cells)
 - Neutropenia (low numbers of neutrophils, a type of white blood cell)
 - Thrombocytopenia (low numbers of platelets)
- A comprehensive metabolic panel—This panel often includes tests for up to 14 chemicals. Chemicals in the blood come from the liver, bones and other organs. Abnormal levels can be caused by cancer or other health problems.
- A beta₂ microglobulin test—Beta₂ microglobulin is a small (micro) protein made by many types of cells, including lymphoma cells. High levels of this protein may be an indication that treatment is needed right away.
- A lactate dehydrogenase (LDH) test—LDH is a protein found in most cells. When a cell is damaged, LDH is released into the bloodstream. Thus, when associated with a cancer, a high LDH level may be a sign that treatment is needed soon.
- Hepatitis testing—The presence of hepatitis B or hepatitis C can be important considerations when treating certain types of lymphoma. Hepatitis B can become active again due to cancer or some of its treatments. Hepatitis C may diminish the effectiveness of therapy.

- Uric acid test—This test measures the amount of uric acid in the body. When cancer cells break down and die, they release substances into the blood. If the cancer cells break down too quickly, the kidneys cannot remove these substances from the blood. An increased level of uric acid can lead to tumor lysis syndrome (TLS). See *Side Effects of Treatment* on page 41.
- Antibody testing—Antibodies, also called “immunoglobulins,” are proteins made by B cells. B cells release antibodies into the blood to help the body fight bacteria and viruses. Depending on the type of NHL, people may have either low or very high levels of tumor-specific antibodies. The quantitative immunoglobulins test measures the amount of each type of antibody. The serum protein electrophoresis (SPEP) test measures specific proteins in the blood.

Bone Marrow Biopsy. Many patients diagnosed with NHL undergo a bone marrow biopsy to make sure the disease has not spread to the bone marrow and to evaluate the potential benefit of certain therapies, including radioimmunotherapy (a combination of radiation therapy and immunotherapy). A bone marrow biopsy may not always be required for patients with early-stage NHL who have low-risk features (eg, no B symptoms and no large masses).

Heart Tests. Some cancer treatments can damage the heart. Members of the treatment team may want to do tests to determine how well a patient’s heart is functioning before starting certain treatments. These tests include

- An echocardiogram—An imaging test that uses ultrasound technology to create a picture of the heart
- A multigated acquisition (MUGA) scan—This scan measures how well the heart pumps blood. A radiotracer substance is injected into a vein. Pictures of the heart are taken with a special camera that detects the radiation released by the tracer.

Other Tests. Some tests are only done for certain NHL subtypes and are therefore not necessary for all patients. Specific examples include

- A full evaluation of the gastrointestinal (GI) tract, including upper and lower endoscopies for patients who have NHL subtypes involving the GI tract, such as mantle cell lymphoma (MCL) and gastric mucosa-associated lymphoid tissue (MALT) lymphoma
- Colonoscopy for patients with MCL (routine colonoscopies are important for everyone beginning at age 50, or earlier if there is a family history of colon cancer)
- Testicular ultrasound for patients who have a testicular mass
- Spinal tap (lumbar puncture) and/or MRI of the brain or spinal column, which may be required for patients with certain subtypes or symptoms that suggest central nervous system involvement.

Staging Systems. The Ann Arbor staging system (see below) and the Lugano modification of the Ann Arbor staging system (see **Table 3** on page 14) are two commonly used methods to stage NHLs.

Table 2. Ann Arbor Staging System for Non-Hodgkin Lymphoma (NHL)

Stage I

- I: Involvement of one lymph node region (eg, the neck)
- IE: Involvement of one organ or area outside the lymph nodes

Stage II

- II: Involvement of two or more lymph node regions, both either above or below the diaphragm
- IIE: Involvement of one or more lymph node region, either above or below the diaphragm, and outside the lymph nodes in an organ or area on the same side of the diaphragm as the affected lymph nodes
- II Bulky: Involvement of multiple lymph node regions on same side of the diaphragm with “bulky disease”*

Stage III

- III: Involvement of lymph node regions above and below the diaphragm (eg, neck, chest and abdomen), with spleen involvement
- IIIE: Involvement of lymph node regions above and below the diaphragm and in a nearby organ or area outside of the lymph nodes
- IIIS: Involvement of lymph node regions above and below the diaphragm and in the spleen
- IIIE+S: Involvement of lymph node regions above and below the diaphragm, outside the lymph nodes in a nearby organ or area, and in the spleen

Stage IV

- Involvement of one or more organs that are not part of a lymphatic area and in lymph nodes near those organs
OR
- Involvement of one organ that is not part of a lymphatic area and in organs or lymph nodes far away from that organ
OR
- Involvement of the liver, bone marrow, cerebrospinal fluid or lungs

Categories

- **E**—“E” stands for extranodal. It means the lymphoma has spread to an area or organ beyond the lymphatic system.
- **S**—“S” stands for spleen and means the lymphoma is found in this organ.
- **X**—“X” indicates “bulky disease.” This refers to a nodal mass that is generally more than 10 cm at its largest point, or more than one third of the chest diameter per x-ray.

The stages and modifying features of NHL.

*Stage II bulky disease is classified as either limited or advanced; this distinction is made on the basis of histology and a number of prognostic factors.

Sources: Adapted from National Comprehensive Cancer Network. Practice Guidelines in Oncology—v.4.2019. B-cell Lymphomas.: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed October 13, 2019. Patel P. Non-Hodgkin Lymphoma Guidelines. Staging. Medscape. Updated June 12, 2019. <https://emedicine.medscape.com/article/2500022-overview#a3>. Accessed October 13, 2019.

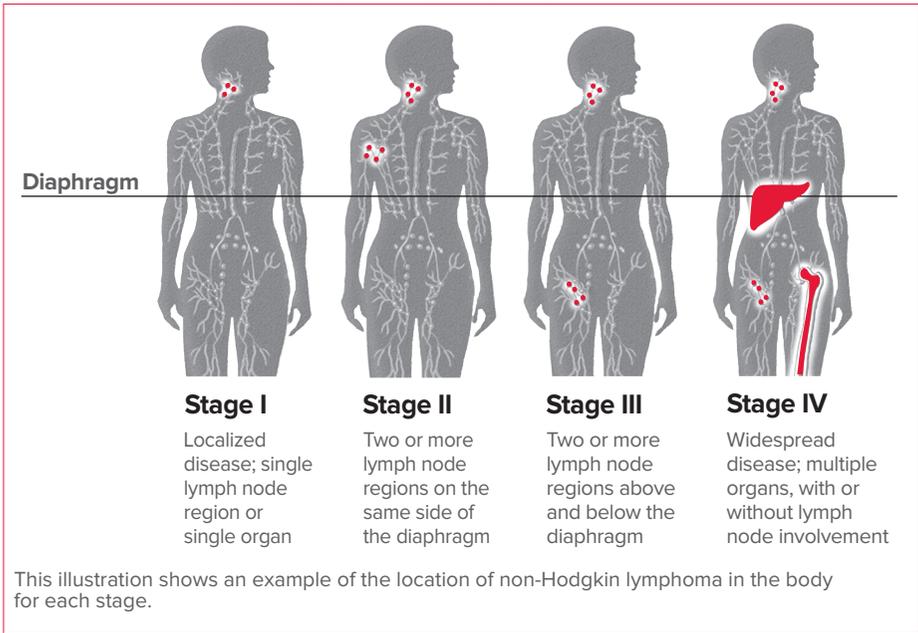
Table 3. Lugano Modification of Ann Arbor Staging System (for primary nodal lymphomas)

Stage	Involvement	Extranodal (E) status
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky	II as above with "bulky" disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm	Not applicable
	Nodes above the diaphragm with spleen involvement	
Stage IV	Additional non-contiguous extralymphatic involvement	Not applicable

Source: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of Clinical Oncology*. 2014; 32(27): 3059-3067.

Keep in mind that “stage IV” does not have the same implications in NHL as it does for many other types of cancer. Non-Hodgkin lymphoma does not necessarily start at stage I and then continue to spread to stage II, and so forth. In lymphoma, the stage identifies the location of the disease. It also does not reflect how well or poorly the patient will respond to treatment. A disease diagnosed as stage IV NHL may be highly treatable, depending on the specific subtype.

Figure 2. Non-Hodgkin Lymphoma (NHL) Stages



When all the diagnostic and staging tests are completed, the doctor will evaluate the information, identify the NHL subtype, determine which areas of the body are involved and begin to discuss treatment options with the patient.

Treatment Overview

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

The initial therapy and intensity of treatment indicated for a patient are based on the subtype and stage of disease. In general, the goal of treatment is to destroy as many lymphoma cells as possible and to induce a complete remission. Complete remission means that all evidence of the disease is eliminated. Patients who achieve remission are sometimes cured. Even when imaging or other studies show remaining sites of disease involvement, treatment can keep the progression of non-Hodgkin lymphoma (NHL) in check for many years. This may be referred to as a “partial remission.”

The watch-and-wait approach (see page 31) may be used for patients who have indolent (slow-growing) subtypes of NHL without signs and/or symptoms. In this approach, treatment is deferred or delayed until signs of disease progression occur. Frequent and careful observation is required so that effective

treatment can be started if the disease starts advancing. In some patients the disease progresses slowly over a long period of time, while in others it evolves (transforms) into a more aggressive type of NHL that requires immediate treatment.

In general, drug therapy (see **Table 4** on page 17) and radiation therapy are the two principal forms of treatment for NHL. Although radiation therapy is generally not the only or the principal curative therapy, it is an important additional treatment in some cases.

Table 5 on page 19 lists examples of drug combinations used to treat NHL. In clinical trials, researchers continue to study the most effective combinations of drugs for the treatment of all types of NHL, including newly diagnosed, refractory and relapsed disease.

Biosimilars. A biosimilar is a biological product that is very similar to another biological drug (called the “reference drug”) that has already received Food and Drug Administration (FDA) approval. Both the reference and biosimilar drugs are made from living organisms, but they may be made in different ways and with slightly different substances. To be called a biosimilar drug, a biological drug must be shown to be as safe and effective as the reference drug, and also work in the same way. It must also be used in the same way, at the same dose and for the same condition as the reference drug. Biosimilar drugs must be approved by the FDA and may cost less than the reference drugs.

Table 4. Some Drugs Used in the Treatment of Non-Hodgkin Lymphoma

Alkylating (DNA-Damaging) Drugs

- Bendamustine hydrochloride (BendeKa®)
- Carboplatin (Paraplatin®)
- Carmustine (BCNU, BiCNU®)
- Chlorambucil (Leukeran®)
- Cisplatin (Platinol®)
- Cyclophosphamide (Cytoxan®)
- Ifosfamide (Ifex®)
- Melphalan (Alkeran®)
- Procarbazine (Matulane®)

Antifolate

- Pralatrexate (FolotyN®)

Antitumor Antibiotics

- Doxorubicin (Adriamycin®)
- Idarubicin (Idamycin®)

Antimetabolites

- Cladribine (Leustatin®)
- Cytarabine (Cytosine arabinoside, ara-C, Cytosar-U®)
- Fludarabine (Fludara®)
- Gemcitabine (Gemzar®)
- Methotrexate (Rheumatrex®, Trexall®)
- 6-thioguanine (Thioguanine Tabloid®)

BCL2 Inhibitor

- Venetoclax (Venclexta®)

Proteasome Inhibitor

- Bortezomib (Velcade®)

DNA Repair Enzyme Inhibitor

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

Drugs That Prevent Cell Division by Blocking Mitosis

- Vinblastine (Velban®)
- Vincristine (Oncovin®)

Hormones That Can Kill Lymphocytes

- Dexamethasone (Decadron®)
- Methylprednisolone (Medrol®)
- Prednisone

Table 4. (cont.)

Immunotherapy

CAR T-Cell Therapy

- Axicabtagene ciloleucel (Yescarta®)
- Tisagenlecleucel (Kymriah®)

Antibody PD-1 Inhibitors

- Mogamulizumab (Poteligeo®)
- Obinutuzumab (Gazyva®)
- Ofatumumab (Arzerra®)
- Pembrolizumab (Keytruda®)
- Rituximab (Rituxan®)
- Rituximab-abbs (Truxima®)
- Rituximab-pvvr (Ruxience™)
- Rituximab + hyaluronidase human (Rituxan Hycela®)

Radioimmunotherapy

- Yttrium-90-ibritumomab tiuxetan (Zevalin®)

Antibody-Drug Conjugates

- Brentuximab vedotin (Adcetris®)
- Polatuzumab vedotin-piiq (Polivy™)

Immunomodulator

- Lenalidomide (Revlimid®)

BTK Inhibitors

- Acalabrutinib (Calquence®)
- Ibrutinib (Imbruvica®)
- Zanubrutinib (Brukinsa™)

HDACs

- Belinostat (Beleodaq®)
- Vorinostat (Zolinza®)
- Romidepsin (Istodax®)

PI3K Inhibitors

- Copanlisib (Aliqopa™)
- Idelalisib (Zydelig®)
- Duvelisib (Copiktra®)

Retinoid

- Bexarotene (Targretin®)

Key. CAR, chimeric antigen receptor; BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; DNA, deoxyribonucleic acid; HDAC, histone deacetylase; PI3K, phosphoinositide 3-kinase; PD-1, programmed cell death protein 1.

Table 5. Some Common Drug Combinations Used in the Treatment of Non-Hodgkin Lymphoma (NHL)

CHOP: cyclophosphamide, doxorubicin (hydroxydoxorubicin), Oncovin® (vincristine), prednisone

B+R: bendamustine hydrochloride (Bendeka®) plus rituximab

R+ICE: rituximab plus ifosfamide, carboplatin, etoposide

R-CHOP: rituximab plus cyclophosphamide, doxorubicin (hydroxydoxorubicin), Oncovin® (vincristine), prednisone

R-HCVAD: rituximab plus cyclophosphamide, vincristine, adriamycin (doxorubicin), dexamethasone

R-EPOCH: rituximab plus adjusted etoposide, prednisone, vincristine (Oncovin®), cyclophosphamide, doxorubicin

DHAP: dexamethasone, high-dose cytarabine (ara-C®) and cisplatin (Platinol®)

ICE: ifosfamide, carboplatin, etoposide

Factors That Influence Treatment. Every patient should discuss treatment options with his or her doctor and ask for help to understand the benefits and risks of different treatment approaches. The most effective treatment plan for each patient with NHL is individualized based on

- The subtype of NHL—knowing whether the lymphoma cells are related to T cells, B cells or natural killer (NK) cells gives the doctor important clues about appropriate treatments
- The stage and category of the disease, which is important information that is factored into treatment decisions (see **Table 2** and **Table 3** on pages 13 and 14)
- The presence or absence of fever, drenching night sweats and loss of more than 10 percent of body weight over 6 months, referred to as “B symptoms”
- Whether there is lymphoma in areas of the body outside of the lymph nodes (extranodal involvement)
- Other prognostic factors, such as age and any underlying medical conditions.

The patient’s age may be a factor, but older age is no longer a major determinant in treatment decisions for most patients. However, the patient’s overall health status, including other medical problems, and also his or her wishes concerning treatment are significant considerations. When making treatment decisions, it is important to discuss effects on fertility and other possible long-term and late effects of treatment.

The International Prognostic Index (IPI). The IPI is a risk-stratification tool that predicts the prognosis of patients who have NHL. Compiled by an international collaboration among several cancer research groups in North America and Europe that evaluated thousands of patients with aggressive forms of NHL, it identifies several unfavorable prognostic factors.

The IPI score is calculated for all patients by totaling the sum of the points scored for each of the risk factors listed below. The score goes from 0 to 5 in the scale reflecting risk factors in patients older than 60 years and from 0 to 3 for the age-adjusted version reflecting risk factors in patients 60 years of age or younger.

Risk factors in patients greater than 60 years (1 point is assigned for each of the following factors):

- Greater than 60 years
- Elevated serum lactate dehydrogenase (LDH) level
- Eastern Cooperative Oncology Group (ECOG) performance status (see **Table 6** on page 21)
- Stage III or IV disease
- Extranodal involvement in two or more sites.

Risk factors in patients less than or equal to 60 years (1 point is assigned for each of the following factors):

- Elevated serum LDH level
- Eastern Cooperative Oncology Group (ECOG) performance status (see **Table 6** on page 21)
- Stage III or IV disease.

The ECOG performance status is determined by a scale used to evaluate a person's ability to perform daily tasks of living without help. See **Table 6** on page 21.

The IPI index helps doctors predict overall survival and the risk of relapse, and provides a basis for recommending whether to use an aggressive or lower-intensity treatment option for high-risk patients.

The number of risk factors a person has determines the IPI risk group they are in. This helps predict his or her risk of relapse. Each point represents some level of increased risk for disease relapse. The following risk categories and corresponding point totals are for patients greater than 60 years:

- Low risk (0 to 1 point)
- Low-intermediate risk (2 points)

- High-intermediate risk (3 points)
- High risk (4 to 5 points).

For patients 60 years of age or younger, the risk categories and corresponding point totals are slightly different. They are

- Low risk (0 points)
- Low-intermediate risk (1 point)
- High-intermediate risk (2 points)
- High risk (3 points).

Patients may want to discuss risk factors with their healthcare team in order to understand their treatment options, including participation in clinical trials.

Table 6. Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Deceased

Source: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*. 1982;5:649-655.

Pretreatment Considerations. Adults of childbearing age and parents of children diagnosed with NHL should ask their doctors for information about possible long-term and late effects, including effects on fertility (the ability to have children) (see *Long-Term and Late Effects of Treatment* on page 44). **For more information about pretreatment considerations, see the free LLS booklets *Fertility and Cancer* and *Long-Term and Late Effects of Treatment in Adults* Facts. Visit www.LLS.org/FamilyWorkbook and the chapter, *Beyond Treatment*, to find information about childhood long-term and late effects.**

Treatment Setting. Patients may undergo treatments over long periods, but most therapies can be administered in an outpatient setting. Radiation therapy, chemotherapy or immunotherapy can be administered in the outpatient clinic of an oncology center.

Short periods of hospitalization are sometimes required. Particularly intensive therapies can cause prolonged or severe decreases in red blood cell, white blood cell and/or platelet counts. Therefore, transfusion of appropriate blood products and administration of cytokines (hormones that enhance blood cell production) may be needed. Outpatient treatment is still possible in some cases that require blood transfusion and/or cytokine treatment. If fever or other signs of infection occur, hospitalization and administration of antibiotics may be necessary. **For more information about transfusion of blood products, see the free LLS booklet *Blood Transfusion*.**

Treatment Considerations for Children, Adolescents and Young Adults.

Non-Hodgkin lymphoma (NHL) accounts for an estimated 5 percent of cancers in children younger than 15 years. Approximately 800 new cases of NHL are diagnosed each year in children and adolescents younger than 20 years. Diffuse large B cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma and anaplastic large cell lymphoma are the predominant NHL subtypes in children ages 5 through 16 years.

Children and adolescents with NHL should be referred to medical centers that have a specialized pediatric oncology team to ensure that they receive optimal treatment, support and follow-up care. Young adults and parents of children diagnosed with NHL should talk to members of the oncology team about the stage and specific subtype of NHL. Doctors use this information to determine the most effective therapy for the patient. It is also important to discuss the planned therapy with members of the oncology team to learn about the drugs that will be used, the potential short- and long-term side effects, including effects on fertility, as well as the treatment schedule. See *Pretreatment Considerations* above.

Different treatment strategies may be used for children than those used for adults with NHL. The choice of therapy for adolescents and young adults can be challenging and is a topic of ongoing research. Pediatric treatment strategies are

used for adults who have certain subtypes of NHL, including Burkitt lymphoma and lymphoblastic lymphoma. Adolescents and young adults should consider being evaluated and treated in a pediatric oncology center, or with a pediatric protocol as part of a clinical trial. With current treatments, NHL is highly curable in most children. The results depend on achieving a precise diagnosis, thorough staging of the disease and using complex, multidrug treatments.

Childhood, adolescent and young adult cancer survivors require close follow-up care because cancer therapy side effects may either persist or develop months, or even years, after treatment. **Visit www.LLS.org/FamilyWorkbook and the chapter, *Beyond Treatment*, to find information about childhood long-term and late effects.**

Treatment of Aggressive Subtypes

Every patient should be evaluated individually by a hematologist-oncologist who specializes in treating non-Hodgkin lymphoma (NHL) and who will discuss the disease subtype, stage and treatment options with him or her. It is also important to receive treatment at a center where the doctors have experience in treating NHL.

Treatment for aggressive B-cell NHL subtypes starts at the time of diagnosis. Patients with fast-growing NHL are generally treated with chemotherapy that consists of four or more drugs. In most cases this is the combination therapy called **R-CHOP** (see **Table 5** on page 19). This intensive, multidrug chemotherapy can be very effective for the treatment of aggressive lymphomas, and cures have been achieved. Chemotherapy can be supplemented by radiation therapy in select cases, for instance, when large NHL masses are found during the diagnostic and staging process.

Diffuse Large B-Cell Lymphoma (DLBCL). This is the most common NHL subtype, accounting for about 31 percent of cases of NHL diagnosed in the United States. It is a cancer of B cells (lymphocytes). Some subtypes of DLBCL originate in B cells found within germinal centers inside lymphatic organs. Germinal centers are short-lived structures formed in response to an outside antigen. Changes occur within the germinal center of B cells in preparation to make antibodies. Other subtypes of DLBCL originate in B cells that have been released from germinal centers.

Diffuse large B-cell lymphoma grows rapidly in the lymph nodes and frequently involves the spleen, liver, bone marrow or other organs. Usually, DLBCL development starts in lymph nodes in the neck or abdomen and is characterized by masses of large B cells. In addition, patients with DLBCL often experience B symptoms (fever, night sweats and loss of more than 10 percent of body weight over 6 months).

For some patients, DLBCL may be their initial diagnosis. For other patients, an indolent lymphoma, such as a small-cell lymphocytic lymphoma or a follicular lymphoma, transforms into DLBCL. Although DLBCL can occur at any age, it most frequently occurs in middle-aged and older persons. Most cases have no known cause.

Gene expression profiling (see page 9) has been used to categorize patients into groups by DLBCL subtype. For example, one group of patients may have different responses to therapy than others; another group may have a different clinical presentation based on the number and types of genes that are either more active or less active in the tumor sample. To date, gene expression profiling studies have distinguished three molecular subtypes of DLBCL based on the cell of origin. They are

- Germinal center B-cell (GCB)
- Activated B-cell (ABC)
- Primary mediastinal B-cell lymphoma (PMBCL).

These distinct DLBCL subtypes arise due to specific genetic changes. Because gene expression profiling is not commercially available, most hematologist-oncologists, working with hematopathologists, will perform immunophenotyping to identify the specific proteins that are associated with either the GCB or the non-GCB subtypes of DLBCL. Therefore, the disease is most commonly classified into GCB and non-GCB subtypes.

According to some studies, DLBCL patients who have the GCB subtype experience significantly better treatment outcomes than those with non-GCB subtypes. A number of clinical trials are under way to investigate whether using novel approaches to therapy improves treatment outcomes for patients with non-GCB subtypes of DLBCL.

The following treatment options are for previously untreated patients:

- **Rituximab (Rituxan®)**, given by IV, is indicated for previously untreated diffuse large B-cell, cluster of differentiation 20 (CD20)-positive NHL in combination with **CHOP** (see **Table 5** on page 19) or other anthracycline-based chemotherapy regimens. R-CHOP can be very effective, and most patients with early-stage DLBCL are cured with this treatment regimen. At this time, there is no standard maintenance treatment for DLBCL. Studies are ongoing to see if maintenance treatment is an appropriate option for these patients.
- **Rituximab and hyaluronidase human (Rituxan Hycela®)** is indicated for previously untreated DLBCL, in combination with CHOP or other anthracycline-based chemotherapy regimens. This drug should be started only after patients have received at least one full dose of a rituximab product by intravenous (IV) infusion before receiving Rituxan Hycela by subcutaneous injection.

Primary mediastinal B-cell lymphoma (PMBCL) is a non-GCB subtype of DLBCL characterized by the overgrowth of scarlike lymph tissue. A tumor generally forms behind the breastbone and may cause coughing and difficulty breathing. The tumor is often very large and can cause pressure on the blood vessels or the heart and lungs. It occurs mainly in young adults around age 35 years and affects slightly more women than men.

Patients with PMBCL often need more intensive treatment than other patients with DLBCL. There are two standard combination regimens: **EPOCH-R** (see **Table 5** on page 19) and **R-CHOP**. EPOCH-R is currently being used more often as a treatment for PMBCL, as there is less need for radiotherapy with this regimen.

Relapsed DLBCL. For patients who experience a relapse, additional chemotherapy (called a “salvage” treatment) is given, which may include drugs that were not used previously. The goal of salvage treatment is to achieve a remission so that it is not necessary to use high-dose chemotherapy or to perform autologous stem-cell transplantation. Treatment options for relapsed DLBCL include

- **Axicabtagene ciloleucel (Yescarta®).** This treatment, given by IV, is an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Axicabtagene ciloleucel is not indicated for the treatment of patients who have primary central nervous system (CNS) lymphoma.
- **Tisagenlecleucel (Kymriah®).** This treatment, given by IV, is a CD19-directed genetically modified autologous T-cell, anti-CD19 chimeric antigen receptor (CAR) immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

For more information about chimeric antigen receptor (CAR) T-cell therapy, see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy*.

- **Pembrolizumab (Keytruda®).** This drug, given by IV, is indicated for the treatment of adult and pediatric patients with refractory PMBCL, or for those whose disease has relapsed after two or more prior lines of therapy. Pembrolizumab is not recommended for treating patients with PMBCL who require urgent therapy to reduce the extent of their disease.

- **Polatuzumab vedotin-piiq (Polivy™).** This drug, given by IV, is a CD79b-directed antibody-drug conjugate that is indicated in combination with bendamustine (Bendeka®) and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.

High-dose chemotherapy and an autologous stem cell transplant (ASCT) may be used to treat patients who relapse after disease remission, but only a minority of patients achieve long-term remissions with this therapy. Allogeneic stem cell transplant remains a potential cure for relapsed DLBCL, but some patients may not qualify for a transplant due to advanced age or the presence of other medical conditions. The efficacy of reduced-intensity transplantation is being evaluated in clinical trials. See *Stem Cell Transplantation* on page 38.

“Double-hit” and “triple-hit” lymphoma. The 2016 revision of the World Health Organization (WHO) classification for lymphoma (see **Table 1** on page 4) included a new category of lymphoma, termed “high-grade B-cell lymphoma with double or triple hits.” This means that this type of lymphoma has translocations involving the *MYC* and *BCL2* and/or *BCL6* genes. “Double-hit” is the term used to describe a lymphoma in which the malignant cells exhibit mutations on two significant genes. These patients have rearrangements (mutations) of the *MYC* gene and either a *BCL2* or a *BCL6* gene rearrangement. When all three rearrangements are present, it is called a “triple-hit” lymphoma. Double- and triple-hit lymphomas account for 6 to 14 percent of DLBCL cases. These lymphoma subtypes do not respond as well to the standard R-CHOP therapy, have an increased risk of central nervous system (CNS) involvement and progression, and the prognosis for patients is unfavorable. B-cell lymphomas that overexpress *MYC* and *BCL2* proteins, but do not have *MYC* and *BCL2* translocations, are called “double expressors.” They are associated with an intermediate prognosis, which falls between double-hit lymphomas and DLCLs without double-hit or double expression. The treatment of double-hit and triple-hit lymphomas has become the focus of ongoing clinical trials.

Acquired Immunodeficiency Syndrome (AIDS)-Associated Lymphoma. The NHL subtypes that occur most frequently in people with AIDS are DLBCL, Burkitt lymphoma and primary central nervous system (CNS) lymphoma. Treatment outcomes are affected by how well the patient with AIDS is responding to treatment and managing the effects of chemotherapy on blood counts. The number of people who develop AIDS-associated NHL has decreased in the last several years because of improved HIV treatments.

Burkitt Lymphoma (BL). This rare and aggressive B-cell subtype grows and spreads very quickly and accounts for about 2 percent of NHL cases. It may involve the jaw, bones of the face, bowel, kidneys, ovaries, marrow, blood, central nervous system and other organs. This disease develops mostly in children and young adults.

Burkitt lymphoma was named after Dr. Dennis Burkitt, a surgeon working in equatorial Africa. There, the disease usually appears in children as a mass in a facial bone, especially the jaw, and signs of Epstein-Barr virus (EBV) are usually found in the lymphoma cells, along with an abnormality of chromosome 8. Burkitt lymphoma occurs far less frequently in other parts of the world. There are three main types:

- Endemic Burkitt lymphoma—the most common form of childhood cancer in Africa, associated with EBV.
- Sporadic Burkitt lymphoma—which occurs throughout the world and accounts for 1 to 2 percent of all adult lymphoma cases in the United States and Western Europe. It is more common in the pediatric population, accounting for 30 percent of lymphoma cases in children. Sporadic cases are associated with EBV, and the most common area of involvement is the abdomen, particularly the intestines.
- Immunodeficiency-related Burkitt lymphoma—often seen in patients with AIDS, individuals with congenital immunodeficiency and in some patients following stem cell transplantation.

Burkitt lymphoma is characterized by the rearrangement of the *MYC* gene caused by a translocation in chromosome 8. This type of lymphoma may spread to the brain and spinal cord (part of the CNS); therefore, prophylactic treatment to prevent it from spreading to the CNS should be included in any treatment regimen for Burkitt lymphoma. CHOP or CHOP-like chemotherapy regimens do not produce favorable results. Instead, a highly aggressive chemotherapy regimen is used to treat this subtype of NHL, often requiring admission to the hospital. Commonly used regimens include

- **CODOX-M/IVAC:** cyclophosphamide, vincristine (Oncovin®), doxorubicin and high-dose methotrexate, alternating with IVAC (ifosfamide, etoposide and high-dose cytarabine)
- **Hyper-CVAD:** hyper-fractionated cyclophosphamide, vincristine, doxorubicin (Adriamycin®) and dexamethasone, alternating with methotrexate and cytarabine (in small studies, rituximab was used in combination with hyper-CVAD)
- **DA-EPOCH-R:** dose-adjusted etoposide, prednisone, vincristine (Oncovin®), cyclophosphamide, doxorubicin plus rituximab

Studies report that BL is curable in a significant group of patients when treated with high-dose, multidrug chemotherapy regimens that include central nervous system (CNS) prophylaxis. About 60 to 90 percent of children and young adults with the disease achieve durable remissions if treated timely and appropriately. Older patients with BL have less favorable outcomes than younger patients.

Patients with relapsed or refractory BL are encouraged to participate in clinical trials. Consolidation treatment with a high-dose conditioning therapy and autologous stem cell transplantation (or allogeneic transplantation, if a donor is available) may be considered for patients who achieve remission after their second-line treatment. See *Stem Cell Transplantation* on page 38. New drugs are currently being evaluated in clinical trials.

Central Nervous System (CNS) Lymphoma. Primary CNS lymphoma forms in the brain and/or the spinal cord. It is often a feature of AIDS-associated lymphoma, but most patients in the United States who have primary CNS lymphoma do not have a clear predisposing cause. Secondary CNS lymphoma develops when a lymphoma already present in other parts of the body spreads to the brain and/or the spinal cord. Patients with highly aggressive lymphomas, such as Burkitt lymphoma and DLBCL, are at a higher risk of disease relapse with CNS involvement. So, first-line treatment for these types of lymphoma may include chemotherapy administered directly into the spinal fluid.

Both primary and secondary CNS lymphomas are uncommon. Treatment options depend on the stage, location of the disease within the CNS, whether the disease has either just been diagnosed or has relapsed, and the patient's age and general health. The options may consist of standard treatment or a therapy being studied in a clinical trial. Standard treatment may include chemotherapy that includes intrathecal **methotrexate**, corticosteroid drugs and/or radiation therapy. Immunotherapy and high-dose chemotherapy with stem cell transplantation are being studied in clinical trials for the treatment of CNS lymphoma. See *Stem Cell Transplantation* on page 38.

Mantle Cell Lymphoma (MCL). This subtype accounts for about 6 percent of all newly diagnosed cases of NHL. Most cases of MCL occur in people over age 60 years, and it is more common in men than in women. In MCL, the malignant cells originate from a lymphocyte in the mantle zone of a lymph node. Mantle cell lymphoma cells express too much of a protein called "cyclin-D1." The disease begins in the lymph nodes and spreads to the spleen, blood, bone marrow and sometimes the esophagus, stomach and intestines. It rarely spreads into the central nervous system.

Patients generally have stage III or IV disease at diagnosis, and most patients need immediate treatment. However, patients with slow-growing MCL do not need treatment right away and may not show signs or symptoms of the disease. Instead, a watch-and-wait approach is used to decide when to start treatment (see *The Watch-and-Wait Approach* on page 31). The standard treatment is a combination chemotherapy regimen, either with or without an autologous stem cell transplant.

Common treatment regimens include bendamustine plus rituximab; a form of CHOP in which bortezomib is used instead of vincristine; and various regimens

including high-dose cytarabine. The following agents are indicated for relapsed and refractory MCL: **acalabrutinib (Calquence®)**, given by mouth; **bortezomib (Velcade®)**, given by IV or subcutaneous injection; **ibrutinib (Imbruvica®)**, given by mouth; **zanubrutinib (Brukinsa™)**, given by mouth; and **lenalidomide (Revlimid®)**, given by mouth.

Allogeneic transplantation with a standard or reduced-intensity conditioning regimen may be considered for patients with relapsed and refractory MCL who achieve remission following second-line therapy. See *Stem Cell Transplantation* on page 38.

For more information about mantle cell lymphoma, including treatment options, see the free LLS booklet *Mantle Cell Lymphoma Facts*.

Peripheral T-Cell Lymphoma (PTCL). This NHL subtype consists of a group of aggressive lymphomas that originate in T lymphocytes. These lymphomas generally occur in people age 60 years and older and are diagnosed slightly more often in men than in women. However, younger adults and children are also sometimes diagnosed with a PTCL. These diseases are rare in the United States. Some forms of PTCL are more common in Asia, Africa and the Caribbean, possibly as a result of exposure to certain viruses, such as the Epstein-Barr virus (EBV) and the human T-cell lymphotropic virus-1 (HTLV-1)

The most common subtypes of PTCL include

- Peripheral T-cell lymphoma, not otherwise specified (PTCL NOS)—This is the most common subtype of PTCL, accounting for about 6 percent of PTCL cases.
- Anaplastic large-cell lymphoma (ALCL)—This subtype usually originates in lymph nodes and can spread to the skin. It accounts for about 2 percent of PTCL cases.
- Hepatosplenic T-cell lymphoma—This uncommon subtype of PTCL generally affects young men.
- Angioimmunoblastic T-cell lymphoma (AITL)—This type of T-cell lymphoma often involves lymph nodes and the bone marrow and is generally associated with viral infection.
- Enteropathy-associated T-cell lymphoma (EATL)—This T-cell lymphoma frequently develops in the small bowel of patients with untreated celiac disease.
- Extranodal natural killer/T-cell lymphoma (ENK/TCL)—This is an uncommon type of lymphoma that can occur in the nasal sinuses or in other parts of the body.

Peripheral T-cell lymphomas are some of the most difficult types of lymphoma to treat. They are generally treated with regimens used for DLBCL, including chemotherapy and other drug therapies.

A number of novel therapeutic agents and regimens in several drug categories are under investigation. In addition, the role of allogeneic stem cell transplantation as part of first-line therapy for patients with high-risk disease, as well as for relapsed and refractory PTCL is being evaluated in clinical trials. See *Stem Cell Transplantation* on page 38 and *Research and Clinical Trials* on page 39.

For more information about peripheral T-cell lymphoma, including treatment options, see the free LLS booklet *Peripheral T-Cell Lymphoma*.

T-Cell Lymphoblastic Lymphoma (T-LBL). Patients with this diagnosis are treated in the same way as patients with acute lymphoblastic leukemia (ALL). **For more information about the diagnosis and treatment of acute lymphoblastic leukemia, see the free LLS booklet *Acute Lymphoblastic Leukemia*.**

Treatment of Indolent Subtypes

The management of indolent lymphoma subtypes at initial diagnosis ranges from observation with careful monitoring (the watch-and-wait approach) to aggressive therapy. Appropriate management is highly individualized and depends on the patient's

- Prognostic factors
- Stage of disease
- Age and other medical conditions

Treatment Options. Standard treatment for indolent NHL subtypes includes the following options:

For early-stage disease

- The watch-and-wait approach
- Radiation therapy
- **Rituximab (Rituxan®)**, with or without chemotherapy

For advanced-stage disease

- The watch-and-wait approach for asymptomatic patients
- Immunotherapy: rituximab, **obinutuzumab (Gazyva®)**, **yttrium-90+ibrutinomab tiuxetan (Zevalin®)**
- Alkylating agents: **cyclophosphamide (Cytoxan®)**, **chlorambucil (Leukeran®)**, **bendamustine hydrochloride (Bendeka®)**
- Combination chemotherapy

The Watch-and-Wait Approach. Many doctors consider observation (the watch-and-wait approach), involving careful monitoring and follow-up care, to be an active form of therapy. Patients need to discuss with their doctors the potential benefits of the watch-and-wait approach, versus initiating chemotherapy and/or other therapies right after diagnosis. Studies comparing the watch-and-wait approach to early treatment have shown no survival advantage in the group of patients who were treated at diagnosis compared to those who were observed.

Some patients with indolent lymphomas need an aggressive initial therapy after diagnosis. However, patients with no symptoms and limited extent of disease can often be observed over long periods of time. Sometimes their condition remains stable for years, and these patients can avoid the side effects of unnecessary therapy during this time. Treatment should start when a patient shows signs of lymphoma progression, such as new or enlarging lymph nodes, bone or other organ involvement, or a decrease in blood cell formation that causes low blood cell counts. The specific decision to treat indolent lymphoma is made collaboratively by the oncologist and patient. Each case is evaluated individually, and treatment approaches vary among patients.

For more information on the watch-and-wait approach, see the free LLS booklet *Watch and Wait*.

Follicular Lymphoma (FL). This is the second most common subtype of NHL, accounting for about 22 percent of newly diagnosed cases of NHL. Most FL cells have a specific chromosome abnormality (a translocation between parts of chromosomes 14 and 18) that causes the overexpression of a gene, *BCL2*, and makes the cells resistant to treatment.

Follicular lymphoma is usually a slow-growing disease. Some patients may not need to start treatment for several years, whereas others have extensive lymph node or organ involvement and need treatment right away. Most patients with FL are age 50 years or older at diagnosis. In a small percentage of patients, FL may transform into a more aggressive disease.

Follicular Lymphoma Treatment. Stage I or stage II FL may be treated with

- The watch-and-wait approach
- Radiation therapy
- Chemotherapy with rituximab (Rituxan®)

Some patients with FL who respond to their initial treatment may be subsequently monitored without any need for further therapy. However, periodic observation continues to be important, so that doctors can identify those who need additional treatment.

For patients who have stage II FL with large lymph nodes, stage III or stage IV FL, or advanced-stage relapsed FL, treatment options will be based on the signs

and symptoms, the patient's age and health status, the extent of disease and the patient's wishes. Those who require treatment may want to consider taking part in a clinical trial.

Other treatment options for FL include

- The watch-and-wait approach
- Radiation therapy to lymph nodes that are causing symptoms, or to a large localized mass, if one is present
- Chemotherapy plus immunotherapy (rituximab)
 - A single chemotherapy drug—for example, **cyclophosphamide, chlorambucil** or **bendamustine hydrochloride (Bendeka®)**—in combination with rituximab
 - A combination chemotherapy plus rituximab, such as **R-CVP**—rituximab plus cyclophosphamide (Cytosan®), hydroxydoxorubicin (doxorubicin), vincristine, prednisone—or **R-CHOP** (see **Table 5** on page 19)
 - Maintenance therapy with rituximab after completion of initial therapy with either rituximab alone or rituximab in combination with chemotherapy. This involves a single dose of rituximab administered on a prescribed schedule, generally every 2 to 3 months, and may be continued for 2 years.
- Autologous and allogeneic stem cell transplantation may be considered for selected patients who have refractory or relapsed FL. See *Stem Cell Transplantation* on page 38.
- Targeted therapy, using kinase inhibitors
 - **Idelalisib (Zydelig®)**—a PI3K kinase inhibitor given by mouth, indicated to treat patients with relapsed follicular B-cell NHL. Idelalisib is intended for patients who have received at least two prior systemic therapies.
 - **Copanlisib (Aliqopa™)**—a PI3K kinase inhibitor given by intravenous (IV) infusion is indicated for adult patients with relapsed FL who have received at least two prior systemic therapies.
 - **Duvelisib (Copiktra®)**—an oral PI3K inhibitor that is indicated for the treatment of adult patients with relapsed or refractory FL after at least two prior systemic therapies. This indication is approved by the FDA under accelerated approval and is contingent upon verification of the clinical benefit of this drug in confirmatory trials.
- **Lenalidomide (Revlimid®)**, an immunomodulator, which is indicated for the treatment of patients with previously treated follicular lymphoma (FL), in combination with a rituximab product. Revlimid is an oral medication that is given in cycles of treatment followed by days of rest.
- Immunotherapy with monoclonal antibodies, either alone or in combination
 - **Yttrium-90-ibritumomab tiuxetan (Zevalin®)**—a cluster of differentiation (CD)20-directed radiotherapeutic antibody, given by IV injection, is

indicated for previously untreated follicular NHL in adult patients who achieve a partial or complete response to first-line chemotherapy, and for relapsed or refractory, low-grade or follicular B-cell NHL.

- **Obinutuzumab (Gazyva®)**—an anti-CD20 monoclonal antibody, given by IV infusion, is indicated in combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV FL. It is also indicated in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL whose disease either relapsed after, or was refractory to, a rituximab-containing regimen.
- The combination of the monoclonal antibody **rituximab and the endoglycosidase hyaluronidase human (Rituxan Hycela™)**—given by subcutaneous injection is indicated for the treatment of
 - Relapsed or refractory FL as a single agent
 - Previously untreated FL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
 - Nonprogressing (including stable disease) FL as a single agent after first-line **CVP** (cyclophosphamide, vincristine, and prednisone) chemotherapy.

This drug should be started only after patients have received at least one full dose of a rituximab product by intravenous (IV) infusion.

The Follicular Lymphoma International Prognostic Index (FLIPI). The FLIPI is a scoring system used to predict which patients with follicular lymphoma may be at higher risk for disease recurrence. This information helps doctors determine appropriate care for patients who have been treated for follicular lymphoma. One point is assigned for each of the following risk factors (known by the acronym NoLASH):

- **N**odes involved—five or more
- **L**actate dehydrogenase (LDH) level—higher than the upper limit of normal
- **A**ge older than 60 years
- **S**tage III or stage IV disease
- **H**emoglobin concentration—less than 12 grams per deciliter (g/dL).

Each point represents an increased risk for disease recurrence. The total number of points determines the risk group, as follows: low risk (0 to 1 point); intermediate risk (2 points); high risk (3 to 5 points). Patients may want to discuss risk factors with their doctor in order to understand their treatment options, including participation in clinical trials.

Transformed B-Cell Follicular Lymphoma (FL). Follicular lymphoma has a small risk of transforming into an aggressive large B-cell lymphoma, such as diffuse large B-cell lymphoma (DLBCL). This occurs in about 15% of patients. Risk factors for transformed FL include advanced-stage disease, high-risk group per FLIPI score, elevated LDH and the presence of B symptoms at initial diagnosis. Patients with transformed B-cell FL appear to benefit from rituximab therapy, either alone or in combination with chemotherapy. Other options include

- **Axicabtagene ciloleucel (Yescarta®).** This treatment, given by IV, is an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Axicabtagene ciloleucel is not indicated for the treatment of patients who have primary central nervous system (CNS) lymphoma.
- **Tisagenlecleucel (Kymriah®).** This treatment, given by IV, is a CD19-directed genetically modified autologous T-cell, anti-CD19 chimeric antigen receptor (CAR) immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

For more information about chimeric antigen receptor (CAR) T-cell therapy, see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy*.

Reduced-intensity transplantation, within a clinical trial, may also be considered in cases of FL transformation. Several novel drug combinations are being studied for the treatment of refractory/relapsed FL.

Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia (WM).

Lymphoplasmacytic lymphoma, accounting for about 2 percent of diagnosed NHL cases, and WM are both slow-growing types of lymphoma that originate in a B-lymphocyte precursor. Waldenström macroglobulinemia is a type of lymphoplasmacytic lymphoma.

In both disorders, malignant lymphoplasmacytic cells are present in the marrow and spleen. These cells share similarities with both plasma cells and lymphocytes. Lymphoplasmacytic lymphoma is usually diagnosed by lymph node biopsy, while WM is diagnosed by marrow examination.

The malignant lymphoplasmacytic cells in both disorders secrete an abnormal protein called “monoclonal immunoglobulin M (IgM).” If the monoclonal IgM levels in the blood become elevated enough, patients experience increased blood

viscosity (thickening of the blood), inadequate blood flow, and symptoms and signs of limited blood flow (eg, headache, visual blurring, mental confusion). This condition, known as “hyperviscosity syndrome,” may require urgent intervention.

One option for patients without symptoms of WM is to adopt the watch-and-wait approach, in which active treatment begins only if symptoms develop. Most patients with WM are treated with chemotherapy combinations that have produced excellent response rates. The Bruton tyrosine kinase (BTK) inhibitor **ibrutinib (Imbruvica®)**, given by mouth, is for the treatment of patients with WM.

For more information about Waldenström macroglobulinemia, see the free LLS booklet *Waldenström Macroglobulinemia*.

Marginal Zone Lymphoma (MZL). This indolent B-cell lymphoma subtype may be extranodal (developing outside of the lymph nodes) or nodal (developing within the lymph nodes). It originates in B lymphocytes in a part of the lymph tissue called the “marginal zone.” The disease tends to remain localized.

There are several subtypes of MZL, each categorized by the type of tissue where the lymphoma forms. They include

- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma—this type of MZL accounts for about 5 percent of diagnosed NHL cases and usually begins in the stomach but it can occur in virtually any mucosal (the moist tissue that lines certain parts of the inside of the body) site in the body. Patients with MALT lymphoma may have a history of autoimmune disease, such as Hashimoto thyroiditis or Sjögren’s syndrome. A higher incidence of MALT lymphoma involving the stomach is seen in patients who have been infected with the bacterium *Helicobacter pylori* (*H pylori*). Other infectious agents have also been implicated in other forms of extranodal MALT lymphoma, such as *Chlamydia psittaci* (*C psittaci*) in the eyes and *Borrelia burgdorferi* (*B burgdorferi*) in the skin.

The disease is generally localized and can often be cured with antibiotics, radiotherapy, chemotherapy and surgery. Many patients with *H pylori* infection have been treated with antibiotics and cured of MALT lymphoma without radiation therapy or chemotherapy. However, the presence of translocation t(11;18) is a predictor of lower likelihood of achieving remission and of an increased risk of relapse. If remission is not achieved following antibiotic treatment, radiotherapy can be a curative option. For a small subset of patients, MALT lymphoma can transform into diffuse large B-cell lymphoma (DLBCL). If this happens, patients can benefit from treatments used for DLBCL.

- Monocytoid B-cell lymphoma—also known as “nodal marginal zone lymphoma” (NMZL), which accounts for about 1 percent of diagnosed NHL cases, may be found in the spleen and blood. This form of NHL is rare and is generally treated like FL.

- Splenic marginal zone lymphoma (SMZL)—accounting for less than 1 percent of all diagnosed NHL cases. Splenic marginal zone lymphoma typically affects patients older than 50 years. This type of lymphoma begins in the spleen and may spread to the peripheral blood and bone marrow. One of the first signs of SMZL is an enlarged spleen; however, symptoms may be slow to develop. It has been associated with hepatitis C infection. Effective treatment may result in remission of the lymphoma.

For patients with SMZL who do not have hepatitis C or any symptoms of lymphoma, the first treatment strategy may be the watch-and-wait approach. Treatment is generally started when an enlarged spleen starts to cause symptoms or produces low white blood cell counts.

For symptomatic patients who are hepatitis-C negative, treatment may include

- Splenectomy (removal of the spleen)
- Single-agent chemotherapy
- Combination chemotherapy plus **rituximab (Rituxan®)**
 - **R-CVP:** rituximab, cyclophosphamide, vincristine and prednisone
 - **R-CHOP** (see **Table 5** on page 19)
 - **B+R:** bendamustine hydrochloride (Bendeka®), rituximab.

For relapsed or refractory cases, treatment may include

- **Ibrutinib (Imbruvica®)**, a Bruton tyrosine kinase (BTK) inhibitor given by mouth, is indicated for the treatment of patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy.
- **Lenalidomide (Revlimid®)**, given by mouth, is indicated in combination with a rituximab product for MZL patients who have been previously treated.

Researchers are evaluating new treatment approaches for MZL. Speak to your doctor or an LLS Information Specialist to find out more about clinical trials.

Chronic Lymphocytic Leukemia (CLL) and Small-Cell Lymphocytic Lymphoma (SLL). Chronic lymphocytic leukemia and SLL are different manifestations of the same disease and their treatment is very similar. Small-cell lymphocytic lymphoma accounts for about 6 percent of diagnosed NHL cases. The major difference between the two diagnoses is that, in CLL, a significant number of the abnormal lymphocytes are found in the blood, in addition to the bone marrow and lymphoid tissues. In SLL, there are few if any abnormal lymphocytes circulating in the blood, and the disease is concentrated in the lymph nodes, bone marrow and other lymphoid tissues.

The following drugs are used to treat newly diagnosed as well as previously treated CLL and SLL:

- **Ibrutinib (Imbruvica®)**, given by mouth
- **Venetoclax (Venclexta®)**, given by mouth
- **Bendamustine hydrochloride (Bendeka®)**, given by IV
- **Obinutuzumab (Gazyva®)**, given by IV, in combination with chlorambucil
- **Acalabrutinib (Calquence®)**, given by mouth.
- **Rituximab (Rituxan®)**, given by IV, in combination with fludarabine and cyclophosphamide

The following drugs are used for cases of relapsed CLL or SLL:

- **Idelalisib (Zydelig®)**, given by mouth, in combination with rituximab or in patients who received at least two prior systemic therapies.
- **Duvelisib (Copiktra™)**, given by mouth, after at least two prior therapies.

The **FCR** (fludarabine, cyclophosphamide and rituximab) regimen is a potentially curative option for some patients with CLL/SLL.

Recent reports from clinical studies indicate that chimeric antigen receptor (CAR) T-cell therapy can induce durable remissions in patients with refractory disease. This therapy is under investigation in clinical trials.

For more information about chronic lymphocytic leukemia, see the free LLS booklet *Chronic Lymphocytic Leukemia*.

Cutaneous T-Cell Lymphomas: Mycosis Fungoides (MF) and Sézary Syndrome (SS). Cutaneous T-cell lymphomas (CTCLs), accounting for about 4 percent of diagnosed NHL cases, are a group of lymphomas that originate in T cells. They develop primarily in the skin and may progress to involve lymph nodes, the blood and other organs. Mycosis fungoides is the most common type of CTCL and it is characterized by prominent skin involvement. It accounts for 50 to 70 percent of all CTCL cases. When the malignant lymphocytes enter and accumulate in the blood, the disease is called “Sézary syndrome.” Sézary syndrome accounts for only 1 to 3 percent of all CTCL cases.

Therapy for CTCL depends on the nature of the skin lesions and whether the disease is present in the lymph nodes. Topical therapies are among the approaches used to treat the skin lesions. These include drugs applied directly to the skin and two therapies based on exposing skin lesions to light—ultraviolet light therapy and electron beam therapy. Ultraviolet light is used in conjunction with **psoralen** (a drug that becomes active when it is exposed to light); this is known as “psoralen and ultraviolet A (PUVA)” therapy. If there is widespread involvement of lymph nodes and other areas, chemotherapy or extracorporeal

photopheresis can be used. Photopheresis is a process in which white blood cells are removed by apheresis, treated with psoralen, exposed to ultraviolet A light and then returned to the patient's bloodstream.

Two histone deacetylase (HDAC) inhibitors, **romidepsin (Istodax®)**, given by IV infusion and **vorinostat (Zolinza®)**, given by mouth, as well as one monoclonal antibody, **mogamulizumab (Poteligeo®)**, given by IV, are indicated for the treatment of adult patients with either relapsed or refractory disease who have received previous systemic therapy.

For more information about cutaneous T-cell lymphoma, see the free LLS booklet *Cutaneous T-Cell Lymphoma*.

Stem Cell Transplantation

The goal of stem cell transplantation is to cure the patient's cancer by destroying the cancer cells with high doses of chemotherapy and then replacing them with new, healthy blood-forming stem cells. The main types of stem cell transplantation are

- Allogeneic—using stem cells from a matched or partially matched donor, either related or unrelated to the patient.
- Autologous—using the patient's own stem cells (taken before the conditioning chemotherapy is given).
- Reduced-intensity—a form of allogeneic transplantation in which patients receive lower doses of chemotherapy drugs and/or radiation therapy in preparation for the transplant.

Autologous stem cell transplantation remains a key component of the standard medical care for patients with aggressive forms of NHL. For indolent lymphomas, autologous stem cell transplantation is primarily used to treat patients with relapsed NHL. Allogeneic transplantation may be considered in the treatment of indolent forms of NHL, particularly for younger patients whose disease behaves more aggressively or has high-risk features.

Stem cell transplantation can cause serious side effects that can be life threatening, so it may not be a treatment option all NHL patients. The risks and benefits of transplantation must always be considered when making treatment decisions. The decision to undergo a transplant should be discussed with the doctor. The doctor will consider many factors, including the patient's age, general health, certain prognostic factors, previous treatments, and if the patient has a well-matched donor.

For more information on stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Research and Clinical Trials

New approaches to non-Hodgkin lymphoma (NHL) treatment are being studied in clinical trials that hold the promise of increasing the rate of remission and finding a cure for NHL. Many of these clinical trials are being supported by LLS research programs.

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

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

Research Approaches. A number of approaches are under study in clinical trials for the treatment of patients with NHL. The following specific examples are some of the treatment approaches and drugs under study:

- Immunotherapy
 - **Ofatumumab (Arzerra®)**—an anticluster of differentiation 20 (anti-CD20) antibody that is approved by the Food and Drug Administration (FDA) for the treatment of relapsed chronic lymphocytic leukemia (CLL). It is being evaluated (administered in various combinations with other medications) for the treatment of mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).
 - **Obinutuzumab (Gazyva®)**—an anti-CD20 antibody already approved by the FDA for CLL treatment. It is currently under study for the treatment of refractory FL, relapsed and refractory CLL, small-cell lymphocytic leukemia (SLL) and indolent lymphomas that do not respond to rituximab.
 - **Blinatumomab (Blincyto®)**—a bispecific antibody that targets CD19 and CD3. It is under investigation for previously treated DLBCL and indolent lymphoma patients.

- **Mogamulizumab (Poteligeo®)**—an antibody targeting chemokine receptor 4 (CCR4) that is FDA approved for the treatment of relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after prior therapy. It is now in clinical trials for various subtypes of NHL, including relapsed or refractory cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL) and DLBCL.
- **Nivolumab (Opdivo®)**—an antiprogrammed death-1 (anti-PD-1) antibody currently being studied for the treatment of relapsed or refractory central nervous system (CNS) lymphoma, FL and DLBCL.
- **Pembrolizumab (Keytruda®)**—already FDA approved for the treatment of refractory or relapsed primary mediastinal large B-cell lymphoma (PMBCL), and now under study for the treatment of DLBCL, PMBCL, FL and other lymphomas.
- **Polatuzumab vedotin-piiq (Polivy™)**—an antibody-drug conjugate targeting CD79b that is FDA approved for the treatment of relapsed and refractory DLBCL. Current trials are exploring its use in combination with other targeted therapies for several types of NHL.
- Phosphoinositide 3-kinase (PI3K) inhibitor
 - **Idelalisib (Zydelig®)**—FDA approved for the treatment of chronic lymphocytic leukemia and refractory indolent NHL. This agent is being explored in combination with chemotherapy and other drugs for the treatment of relapsed or refractory indolent B-cell NHL, mantle cell lymphoma (MCL) and marginal zone lymphoma.
 - **Umbralisib (TGR-1202)**—an oral, once daily, dual inhibitor of PI3K delta and CK1 epsilon is being studied in patients with CLL and NHL.
- Bruton Tyrosine Kinase (BTK) Inhibitor
 - **Ibrutinib (Imbruvica®)**—a BTK inhibitor already approved by the FDA for the treatment of several types of NHL. It is being evaluated for the treatment of patients with relapsed and refractory, non-GCB subtypes of DLBCL who are not candidates for autologous stem cell transplantation.
- mTOR Inhibitor
 - **Temsirolimus (Torisel®)**—an inhibitor that blocks a protein involved in cell division. It is currently under study for relapsed and refractory DLBCL.
- Other Agents
 - The oral **selective inhibitor of nuclear export (SINE), selinexor (KPT-330)**—an inhibitor that is currently being evaluated for the treatment of DLBCL. This drug acts by blocking the transport of nuclear proteins in malignant cells, leading to cell death.
 - **CPI-613® (devimistat)**—an antimitochondrial metabolism agent that blocks the mitochondrial cycle used by cancer cells to survive and multiply. It is being evaluated in trials for treating refractory or relapsed Burkitt lymphoma.

- **Tazemetostat**—a first-in-class small molecule EZH2 inhibitor given by mouth, is currently in clinical trials for relapsed/refractory non-Hodgkin lymphoma.
- **Chimeric antigen receptor (CAR) T-cell therapy**—a type of immunotherapy that consists of engineering a patient’s own immune cells to recognize and then attack cancerous tumor cells. **Axicabtagene ciloleucel (Yescarta®)** and **tisagenlecleucel (Kymriah®)** are FDA approved for the treatment of relapsed and refractory DLBCL. Several ongoing studies of CAR T-cell therapy targeting CD19 are evaluating the effectiveness of this therapy for treating refractory and relapsed NHL.

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

- **Reduced-Intensity Stem Cell Transplantation (Nonmyeloablative Allogeneic Transplantation)**—a type of transplantation that is a potential option for older and sicker patients. Studies are under way to evaluate and determine its effectiveness as treatment for many blood cancers, including some NHL subtypes. Patients undergoing a reduced-intensity transplant receive lower doses of chemotherapy drugs and/or radiation therapy in preparation for the transplant. The effectiveness of reduced-intensity transplantation is due to the graft-versus-lymphoma effect of the donor’s lymphocytes rather than to high doses of chemotherapy.

Contact our Information Specialists and visit www.LLS.org/CTSC for more information about finding a clinical trial.

Side Effects of Treatment

The side effects of treatment for lymphoma depend on the intensity and type of treatment and other factors, such as which area(s) of the body radiation therapy is used, the patient’s age and his or her coexisting medical conditions (eg, diabetes mellitus and chronic renal disease). In addition, certain drugs have a tendency to affect certain tissues—for example, **vincristine** typically affects nerve tissue.

In recent years, new drugs and other therapies have increased doctors’ ability to control side effects that are troublesome for many patients, such as nausea and vomiting. When side effects do occur, most are short-term and resolve when therapy is completed. The benefits of receiving treatment for non-Hodgkin lymphoma (NHL), with the goal of remission (and in some cases, cure), generally outweigh the associated risks and discomfort.

Suppressed Blood Cell Formation. Decreases in blood cell counts may occur in patients treated with chemotherapy. Blood transfusions may be necessary for some patients with low blood cell counts. If decreases in white blood cell counts are severe and continue over extended periods of time, an infection may

develop and require antibiotic treatment. Sometimes, chemotherapy dosages or the time between chemotherapy cycles must be altered to allow the patient's blood cell counts to recover from the effects of treatment. A granulocyte-colony stimulating factor (G-CSF), such as **Neupogen®** or **Neulasta®**, is sometimes used to stimulate the production of white blood cells when they are depleted. It is given by subcutaneous injection to increase the number of white blood cells that help prevent infection.

Infections. Chemotherapy and radiation therapy can make patients more susceptible to infection because these treatments weaken immune cell function and can lower the number of normal white blood cells. Removal of the spleen, a treatment option for patients with some types of NHL, such as splenic marginal zone lymphoma, also contributes to the risk of severe infection.

Infections can be very dangerous. It is very important to take fevers seriously and get to the hospital if you have a fever of over 100.4° F.

Patients with NHL are advised to receive certain vaccinations, including vaccinations for pneumococcal pneumonia and influenza, once they have finished their treatment. There are two types of pneumococcal vaccines available for adults: a **pneumococcal polysaccharide vaccine (PPSV23)** and a **pneumococcal conjugate vaccine (PCV13)**. Patients with NHL should not be given vaccines that use live organisms or those with high viral loads, such as the herpes zoster (shingles) vaccine, but they can receive **Shingrix®** because it is an inactivated shingles vaccine. Your doctor can give you more information.

Viral Reactivation. Hepatitis B virus (HBV or Hep B) reactivation has been reported in some patients treated with chemotherapy, either with or without immunotherapy drugs. Carriers of the hepatitis B virus, especially those treated with anticancer of differentiation 20 (anti-CD20) monoclonal antibodies, including **rituximab (Rituxan®)**, **ofatumumab (Arzerra®)** and **obinutuzumab (Gazyva®)**, have a high risk of virus reactivation and disease.

Preventive antiviral therapy is recommended for patients who test positive for HBV if they are going to receive an NHL therapy. Cytomegalovirus (CMV) reactivation may occur in patients with chronic lymphocytic leukemia (CLL) or small-cell lymphocytic lymphoma (SLL) receiving **alemtuzumab (Campath®)** therapy. This occurs most frequently between 3 to 6 weeks after the start of therapy, when T-cell counts reach their lowest point. This complication happens in up to 25 percent of treated patients. Current practices to prevent the CMV reactivation include the use of a prophylactic antiviral drug (**ganciclovir**), to be administered if the patient tests positive for CMV prior to alemtuzumab treatment. Patients being treated with regimens containing alemtuzumab should be monitored frequently for the virus (every 2 to 3 weeks) during the treatment and for 2 months after the completion of therapy.

Bone Loss and Fractures. Drug regimens that contain corticosteroids have been associated with an increased risk of fractures and treatment-induced bone loss in patients with NHL. The risk of bone loss is higher among young women with chemotherapy-induced premature menopause and older patients receiving chemotherapy. In addition, patients with newly diagnosed NHL are also at risk of low bone mineral density, which may worsen during treatment with systemic corticosteroids. Evaluation of vitamin D levels and of post-treatment bone loss is recommended for patients receiving this type of therapy. Patients should also maintain an adequate calcium intake since corticosteroids block calcium absorption and increase the risk of fractures. **Pamidronate** and **zoledronic acid** are part of a group of drugs called “bisphosphonates.” These drugs can help stabilize bone mineral density, prevent bone loss and reduce the risk of new fractures in patients with NHL.

Neuropathy. Some chemotherapeutic agents, such as **vincristine (Oncovin®)** or **brentuximab vedotin (Adcetris®)**, can cause nerve damage called “neuropathy.” Initially, the patient experiences numbness and tingling in the fingertips and toes. The sensation might be temporary, but if it continues, it may become permanent. In general, treatment options are limited. The patient should be monitored for these side effects between each cycle of chemotherapy that includes vincristine. If the neuropathy becomes severe, the drug dosage may need to be adjusted.

Tumor Lysis Syndrome. Patients with NHL, especially those with very high white blood cell counts before the beginning of treatment, may be at high risk for developing acute tumor lysis syndrome (TLS). This condition is characterized by metabolic abnormalities caused by the sudden release of the cellular contents of dying cells into the bloodstream that the kidneys cannot remove. If untreated, TLS can lead to heart arrhythmias, seizures, loss of muscle control, acute kidney failure and even death. Patients with a high level of uric acid may be given the drug **allopurinol (Zyloprim®)** to minimize the buildup of uric acid in the blood. Allopurinol is taken by mouth. Another drug, **rasburicase (Elitek®)**, is given in a single intravenous dose and can rapidly lower an elevated uric acid level.

Progressive Multifocal Leukoencephalopathy (PML). This is a very rare but serious and potentially fatal central nervous system infection caused by the reactivation of the latent John Cunningham (JC) virus. Cases of PML typically occur in severely immunocompromised individuals, such as acquired immunodeficiency syndrome (AIDS) patients or blood cancer patients who have profound immunosuppression due to the underlying disease or its treatment.

The use of rituximab, in combination with chemotherapy, may be associated with an increased risk of PML in immunocompromised patients with CLL/SLL and other types of NHL. Signs and symptoms of PML include confusion, poor

coordination, motor weakness and visual and/or speech changes. To date, there is no effective treatment for this condition. Patients at risk should be carefully monitored for the development of any neurological symptoms.

Other Side Effects. Chemotherapy affects tissues that normally have a high rate of cell turnover, so it may affect the lining of the mouth, the lining of the intestines, the skin and the hair follicles. Common side effects of therapy include

- Mouth sores
- Nausea and vomiting
- Diarrhea
- Temporary hair loss
- Fatigue
- Cough
- Fever
- Rash.

These side effects can range from mild to severe. They depend on the medications and dosages used and the individual patient's susceptibility. Fortunately, there are drugs and other supportive measures to either prevent or manage many side effects.

Children may experience side effects of treatment for a short time or for longer periods that can affect learning. **For more information about how side effects can affect children, see the free LLS booklet *Learning & Living With Cancer: Advocating for your child's educational needs.***

Long-Term and Late Effects of Treatment

Long-term effects of cancer therapy are medical problems that persist for months or even years after treatment ends. Late effects are medical problems that do not develop or become apparent until years after treatment ends.

It is important to know about the potential for long-term and late effects of treatment so that any problems may be identified early and managed. Various factors can influence the patient's risk, including

- Type and duration of treatment
- Age at time of treatment
- Gender and overall health.

Many survivors of non-Hodgkin lymphoma (NHL) do not develop significant long-term or late effects of treatment. However, it is important for all adult patients, as well as the parents of children who will be treated for NHL, to discuss possible long-term and late effects with members of the treatment team so that the proper planning, evaluation and follow-up care can take place.

Heart Disease. Radiation therapy to the chest and treatment with chemotherapy containing alkylating agents (eg, **cyclophosphamide**) or anthracyclines (eg, **doxorubicin**) have been linked to heart disease. This includes inflammation of the sac surrounding the heart (the pericardium), valve dysfunction or a classic heart attack (myocardial infarction).

Secondary Cancers. For as long as 3 decades after diagnosis, patients are at a significantly elevated risk for second primary cancers, such as lung, brain and kidney cancers, melanoma and Hodgkin lymphoma. Autologous bone marrow or peripheral blood stem cell transplantation and treatment with chemotherapy containing alkylating agents are associated with an increased risk of myelodysplastic syndromes and acute myeloid leukemia.

Fertility. Patients may have decreased fertility after treatment for NHL. The risk of infertility varies according to the nature of the treatment, including the type and amount of chemotherapy, which area(s) of the body radiation therapy is used and the patient's age. Male patients who are at risk of infertility should consider sperm banking before treatment, and female patients should discuss all of their fertility preservation options. Women who have ovarian failure after treatment experience premature menopause and require hormone replacement therapy.

It is important to discuss all your options and treatment concerns with your doctor. If possible, you may also want to discuss these options with a doctor who specializes in fertility and reproduction. Many cancer centers have reproductive specialists who will suggest specific options for each patient. For couples of childbearing age in which one partner has received treatment, the incidence of pregnancy loss and the health of a newborn are very similar to those of healthy couples.

For more information about fertility, see the free LLS booklets *Fertility and Cancer*. Visit www.LLS.org/FamilyWorkbook and the chapter, *Beyond Treatment*, to find information about childhood long-term and late effects.

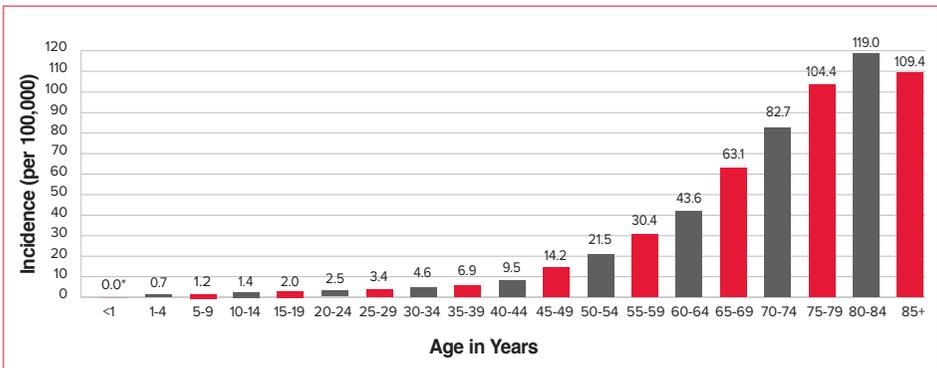
Follow-up Care. Follow-up care is important for patients who have NHL. If the disease recurs, many treatment options are still available. Follow-up care needs to be individualized and should be based on several factors, including how the disease initially manifested. Patients whose disease is in remission should continue to be monitored by clinical assessment as determined by their doctor. In the past, computed tomography (CT) or other diagnostic imaging scans were done routinely in an attempt to detect relapse. However, there is an increasing awareness that undergoing too many scans may be harmful, and that CT scans performed in otherwise asymptomatic patients have a relatively low likelihood of finding recurrent lymphoma. The frequency of clinical visits, laboratory tests and CT scans or other imaging tests should be discussed with the treating doctor.

Periodic assessment of the patient’s state of health, blood cell counts and, if indicated, bone marrow is important. Over time, the interval between assessments may be lengthened, but assessments should be continued indefinitely for most patients.

Incidence, Causes and Risk Factors

Incidence. About 74,200 new cases of non-Hodgkin lymphoma (NHL) were expected to be diagnosed in the United States in 2019. Non-Hodgkin lymphoma occurs in individuals at virtually all ages, but it is uncommon in children. The disease is more common in men than women, and among whites. It is most frequently diagnosed in people 80 to 84 years old (see **Figure 3** below).

Figure 3. Age-Specific Incidence Rates for Non-Hodgkin Lymphoma, 2011-2015



The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of non-Hodgkin lymphoma each year per 100,000 people, by age-group. The incidence of non-Hodgkin lymphoma significantly increases with age. Fewer than 7 cases per 100,000 occur in people in their late 30s. Incidence increases progressively to 119.0 cases per 100,000 in persons age 80 to 84.

Source: The Leukemia & Lymphoma Society. Facts 2018-2019.

Causes and Risk Factors. The exact cause of NHL is not known, but there are risk factors that may increase the likelihood of developing the disease. Factors affecting people’s risk of developing NHL have been studied extensively. Some of these factors are immune disorders, medicines, infections, lifestyle, genetics, race, family history and occupational factors.

- Obesity has been found to be a risk factor for diffuse large B-cell lymphoma (DLBCL).
- Genomewide-association studies, an approach used in genetics research to associate specific genetic variations with particular diseases, have found loci (meaning the position of a gene or mutation on a chromosome) that are associated with excessive risk for follicular lymphoma, marginal zone lymphoma and DLBCL.
- Immune suppression is one of the most clearly established risk factors for NHL. People with autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, acquired immunodeficiencies including HIV/AIDS, and organ transplant recipients have an elevated risk for NHL. Whether this increased risk is related only to the immune disease, or to the immunosuppressive therapies employed to treat it, is not clear.
- A number of occupational and environmental factors have also been associated with NHL. Farming communities have a higher incidence of NHL, and farm work has been linked to major NHL subtypes and to NHL overall. This observation has led to research on agricultural chemicals, such as pesticides, solvents, fuels, oils and other agents that are potentially carcinogenic.

Some studies suggest that specific substances in herbicides and pesticides, such as organochlorine, organophosphate and phenoxy acid compounds, are linked to lymphoma. For example, the occupational exposure to non-arsenic insecticides during spraying and application has been classified by the International Agency for Research on Cancer as a “probable human carcinogen” for NHL. Data from a recent study from the University of Washington has indicated that people who have high exposure to the glyphosate herbicide Roundup®, used to kill weeds, have an increased risk of developing NHL.

The number of lymphoma cases caused by exposures to herbicides and pesticides has not been determined. More studies are needed to understand these associations.

- Exposure to certain viruses and bacteria is associated with NHL. It is thought that being infected with either a certain virus or bacterium can lead to rapid lymphoid cell reproduction, increasing the probability of a cancer-causing event in a cell. Here are some examples:
 - Epstein-Barr virus (EBV) infection in patients from specific geographic

regions in Africa is strongly associated with Burkitt lymphoma. The role of the virus is unclear, since Burkitt lymphoma in Africa also occurs among people who have not been infected with EBV.

- Epstein-Barr virus infection may also play a role in the increased risk of NHL in people with a suppressed immune system as a result of organ transplantation and its associated therapy. EBV infection is closely associated with both Burkitt lymphoma and nasal natural killer (NK/T-cell lymphoma).
- Human T-cell lymphotropic virus-1 (HTLV-1) is associated with a type of T-cell lymphoma in patients from certain geographic regions in southern Japan, the Caribbean, South America and Africa.
- HIV/AIDS is associated with the development of certain types of NHL that generally occur in older patients.
- The bacterium *Helicobacter pylori* (*H pylori*) causes ulcers in the stomach and is associated with the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma in the stomach wall.
- Hepatitis C is associated with the development of splenic marginal zone lymphoma and DLBCL. Associations with other types of lymphoma are being explored.
- The bacteria *Borrelia burgdorferi* (*B burgdorferi*) and *Chlamydia psittaci* (*C psittaci*) are thought to be associated with the development of marginal zone lymphomas.
- The bacterium *Coxiella burnetti* (*C burnetti*) has been proposed as a risk factor for DLBCL and follicular lymphoma.
- The risk factors identified for peripheral T-cell lymphomas include celiac disease, eczema, psoriasis, an extensive smoking history, and working with textiles or electrical equipment.
- Other conditions, such as Sjögren syndrome, Wiskott-Aldrich syndrome and Klinefelter syndrome, can predispose individuals to later development of NHL. These inherited disorders are uncommon, but the concept of predisposition genes is under study to determine if they play a role in the random occurrence of NHL in otherwise healthy individuals.

For more information, contact an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/resourcedirectory (click on “Disease registries and other disease studies” under “Blood Cancer—General Information.”)

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

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

- Proteins
 - Albumin. This is the most common blood protein.
 - Blood-clotting proteins (coagulation factors). They are made by the liver.
 - Erythropoietin. It is made by the kidneys and stimulates red blood cell production.
 - Immunoglobulins. These are cells that fight infection.
- Hormones, such as thyroid and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B₁₂
- Electrolytes, such as calcium, potassium and sodium.

Blood cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." The blood cells are suspended in the plasma. See **Figure 4** on page 50.

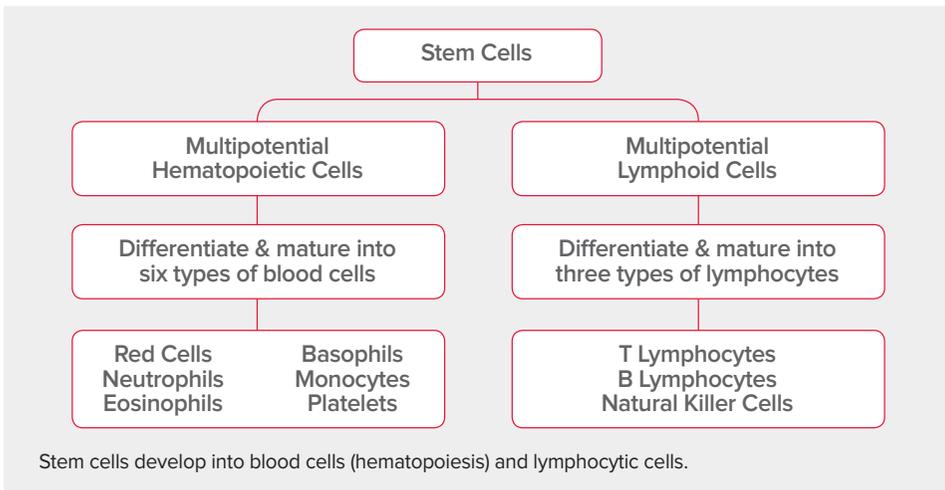
Once the blood cell is created, it will develop into one of the three types of blood cells.

These are

1. Red blood cells (the cells that carry oxygen); they
 - Make up a little less than half of the body's total blood volume
 - Are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO₂) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO₂ is removed from the lungs.
2. Platelets (cells that help blood clot); they
 - Are small cells (one-tenth the size of red blood cells)
 - Help stop bleeding from an injury or cut
 - Stick to the torn surface of the vessel, clump together, and plug up the bleeding site. They form a clot, with the help of proteins, such as fibrin, and electrolytes, such as calcium.

3. White blood cells (WBCs) are cells that fight infections. The several types of WBCs include
- Neutrophils and monocytes: These are “phagocytes” (eating cells) that ingest and destroy bacteria and fungi. Unlike red cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
 - Eosinophils and basophils: WBCs that respond to allergens or parasites.
 - Lymphocytes: WBCs found mostly in the lymph nodes, spleen and lymphatic channels, they are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
 - T lymphocytes (T cells)
 - B lymphocytes (B cells)
 - Natural killer (NK cells)

Figure 4. Blood Cell & Lymphocyte Development



In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the marrow and then circulates throughout the body.

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone, and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be transplanted. Some stem cells enter the bloodstream and circulate; there are not enough of them to be counted in standard blood tests. Doctors know how to stimulate the growth of these cells in the marrow and have them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

The Lymphatic System

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

The marrow produces three main types of lymphocytes. They are

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

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

Resources and Information

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

For Help and Information

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

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

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

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

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

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Please visit www.LLS.org/finances for more information.

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

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

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format

and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Please visit www.LLS.org/HealthManager to download for free.

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

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

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

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

Community Resources and Networking

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please visit www.LLS.org/community to join.

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

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

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

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to obtain our directory.

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

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

Additional Help for Specific Populations

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

Language Services. Let members of your healthcare team know if you need a language interpreter or other assistance, such as a sign language interpreter. Often, these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please

- Call: the VA (800) 749-8387 (select option 4)
- Visit: www.publichealth.va.gov/exposures/AgentOrange

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

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

For more information, please

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

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. For more information, please

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov. Enter “depression” in the search box.

Health Terms

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. A type of allogeneic transplant called “reduced-intensity” or “nonmyeloablative” transplant is under study. It uses lower doses of chemotherapy and/or radiation therapy for the conditioning therapy and may therefore be safer, especially for older patients. **For more information about allogeneic stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Anemia. A decrease in the number of red blood cells and, therefore, the hemoglobin concentration of the blood. This results in a diminished ability of the blood to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue and shortness of breath on exertion.

Antibodies. Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to specific foreign substances called “antigens.” Antibodies coat, mark for destruction or inactivate foreign particles, such as bacteria, viruses or harmful toxins.

Antigen. A foreign substance, usually a protein, that stimulates an immune response when it is ingested, inhaled or comes into contact with the skin or mucous membranes. Examples of antigens are bacteria, viruses or allergens. Antigens stimulate plasma cells to produce antibodies.

Apheresis. The process of removing certain components of a donor's blood and returning the unneeded parts back to the donor's bloodstream. The process uses continuous circulation of blood from a donor through a specialized machine and then back to the donor through an intravenous line. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red blood cells, white blood cells and plasma can be removed separately.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. The autologous transplantation process takes place after the patient achieves a complete response (remission), or a good partial response, to induction drug therapy. **For more information, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Biopsy. A procedure that is used to obtain tissue samples for diagnostic tests. In many cases, a special needle can be used to obtain the tissue. In some cases, a larger piece of tissue may be surgically removed. Since

the appearance of a lymph node is important in categorizing the type of lymphoma that may be present, surgical removal of an entire, swollen lymph node or multiple nodes may be necessary (lymph node biopsy).

Bone Marrow. A spongy tissue in the hollow central cavity of the bones, where blood cell formation occurs. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. The marrow is filled with fat cells in other sites. When marrow cells have matured into blood cells, they enter the blood as it passes through the marrow and then are carried throughout the body in the bloodstream.

Bone Marrow Aspiration. A procedure in which a small sample of bone marrow is removed, usually from the hip bone. A small area of skin and the surface of the bone underneath are numbed with an anesthetic. Then, a special wide gauge needle is pushed into the bone. A sample of liquid bone marrow is removed with a syringe attached to the needle. The specimen of bone marrow is sent to a laboratory to be looked at under a microscope. This procedure may be done at the same time as a bone marrow biopsy.

Bone Marrow Biopsy. A test to examine marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip (pelvic) bone. After a local anesthetic is given to numb the skin, a special hollow biopsy needle is used to remove a core of bone containing marrow. The marrow sample is examined under a microscope to determine if abnormal cells are present. Bone marrow aspiration and bone marrow biopsy are almost always done together.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Transplantation.

CD. See Cluster of Differentiation (CD).

Chemotherapy. The use of chemicals (drugs or medications) to kill malignant cells. Numerous chemicals have been developed for this purpose, and most act by injuring the DNA (deoxyribonucleic acid) of the cancer cells. When the DNA is injured, the cells cannot grow or survive.

Chromosomes. Threadlike structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes: chromosome pairs 1 to 22 and one pair of sex chromosomes (XX for females and XY for males). See Translocation.

Clonal. The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers originate in a single cell with an injury (mutation) to its DNA (deoxyribonucleic acid) and are therefore monoclonal. Leukemia, lymphoma and myeloma are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Cluster of Differentiation (CD). A term used with a number to identify a specific molecule on the surface of an immune cell. It is commonly used in its abbreviated form—for example, “CD20,” the target of the monoclonal antibody therapy rituximab (Rituxan®) and “CD52,” the target of the monoclonal antibody therapy alemtuzumab (Campath®). Also called “cluster designation.”

Colony-Stimulating Factor. See Growth Factor.

Computed Tomography (CT) Scan. A technique for imaging body tissues and organs. X-ray transmissions are converted to detailed images using a computer to synthesize x-ray data. The images are displayed as a cross-section of the body at any level from the head to the feet. A CT scan of the chest, abdomen or pelvis permits detection of an enlarged lymph node, liver or spleen. A CT scan can be used to measure the size of these organs and other structures both during and after treatment.

CT Scan. See Computed Tomography Scan.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes of cells. It detects chromosome alterations and, in some cases, may identify the actual genes that have been affected. These findings help healthcare professionals diagnose specific types of blood cancers, determine treatment approaches and monitor the response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a “cytogeneticist.”

Differentiation. The process by which stem cells give rise to functional cells from a single blood cell line. Differentiation of stem cells forms the red blood cells, platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils and lymphocytes). See Hematopoiesis.

DNA. Abbreviation of “deoxyribonucleic acid,” the genetic material in cells. It is made up of a sugar-phosphate backbone with ladderlike “steps” composed of purines and pyrimidines (the building blocks of nucleic acids). The sequence of the purines and pyrimidines in the DNA (deoxyribonucleic acid) is responsible for passing genetic

information to new cells during the process of cell division; for passing genetic information from one generation to the next during reproduction; and for providing the instructions for building proteins, which in turn carry out the major functions of a cell. A mutation is generally either a change in or loss of the sequence of the purines or pyrimidines of the DNA. Mutations can lead to cell death, to changes in the way a cell functions or, in some cases, to cancer.

Eosinophil. A type of white blood cell that participates in allergic reactions and helps fight certain parasitic infections.

Erythrocytes. See Red Blood Cells.

Extranodal Lymphoma. Lymphoma that has spread outside the lymph nodes to the organs—the thyroid, lungs, liver, bones, stomach or central nervous system. Doctors adjust their therapeutic approach if organs outside of lymph nodes are involved. If the brain, liver or bones are involved, for example, the treatment approach is likely to target these areas. If lymphoma is found in any of the organs but not in lymph nodes or multiple lymphatic sites, the disease is called a “solitary extranodal lymphoma.”

FDA. The acronym for The United States Food and Drug Administration.

FISH. See Fluorescence In Situ Hybridization.

Flow Cytometry. A laboratory method that measures the number of cells, the percentage of live cells, and certain characteristics of cells, such as size and shape, in a sample of blood, bone marrow, or other tissue. The presence of tumor markers, such as antigens, on the surface of the cells are also measured. The cells are stained with a light-sensitive dye, placed in a fluid, and then passed one at a time through a beam of light. The measurements are based on how the stained cells react to the beam of light. One use of flow cytometry is to determine whether a sample of cells is composed of T cells or B cells. This allows the doctor to determine if the leukemia or lymphoma is of the B- or T-cell type.

Fluorescence In Situ Hybridization (FISH). A technique for studying chromosomes in tissue samples using DNA (deoxyribonucleic acid) probes tagged with fluorescent molecules that emit light of different wavelengths and in different colors. The probes bind to the chromosomes within the cells, and the chromosomes fluoresce in color.

G-CSF (Granulocyte-Colony Stimulating Factor). See Growth Factor.

Gene Expression Profiling. A research method that uses microarray analysis to identify a combination of genes that are either deactivated or activated in response to a specific condition. A set of genes in a blood or tissue sample can be used to monitor the levels of thousands of genes at once.

GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor). See Growth Factor.

Granulocyte. A type of white blood cell that has a large number of granules in the cell body. Neutrophils, eosinophils and basophils are types of granulocytes.

Growth Factor. A chemical used to stimulate the production of neutrophils and shorten the period of low neutrophil counts in the blood after chemotherapy. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are examples of growth factors that are made commercially. Granulocyte-macrophage colony stimulating factor can also stimulate monocytes.

Hematologist. A doctor who specializes in the treatment of blood cell diseases. This person is either an internist who treats adults or a pediatrician who treats children.

Hematopathologist. See Pathologist.

Hematopoiesis. The process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells, which start the process of blood cell development. The stem cells begin to develop into immature (undeveloped) blood cells, such as red blood cells or various types of white blood cells. This process is called “differentiation.” The immature blood cells then further develop into fully functional blood cells. This process is called “maturation.” The mature cells leave the marrow, enter the blood and circulate throughout the body in the bloodstream. Hematopoiesis is a continuous process that is normally active throughout life. When the marrow is invaded with cancer cells, the constant demand for new blood cells cannot be met, resulting in a severe deficiency in blood cell counts.

Immunophenotyping. A method that uses the reaction of antibodies with cell antigens to identify specific types of cells in a sample of blood, marrow or lymph node cells. The antibodies react with specific antigens on the cell. A tag is attached to an antibody so that it can be detected by

the laboratory equipment used for the test. As cells carrying their array of antigens are tagged with specific antibodies, they can be identified.

Immunotherapy. The term for several treatment approaches used by doctors to harness the body's immune system to treat lymphoma and other diseases. These therapies include monoclonal antibody therapy, radioimmunotherapy and vaccine therapy. Monoclonal antibodies are proteins made in the laboratory that either react with or attach to antigens on the target cells. The antibodies are used therapeutically in three ways: as "naked" antibodies (monoclonal antibodies); as antibodies to which radioactive isotopes are attached (radioimmunotherapy); and as antibodies to which toxins are attached (immunotoxins). **For more information, see the free LLS booklet *Immunotherapy*.**

Intrathecal. Designation for the space between the covering or lining of the central nervous system (CNS) and the brain or spinal cord, which is called the "meninges." In some situations, drugs have to be administered directly into the spinal canal when cancer cells are present in the meninges. This procedure is called "intrathecal therapy."

Lactate Dehydrogenase (LDH). An enzyme present in all normal and abnormal cells. It is released from cells into the blood and is present in normal amounts in the liquid portion of blood (the plasma). When blood is collected and allowed to clot, the fluid portion is called the "serum." Many chemicals can be measured in the serum, including LDH. Normal serum contains low levels of LDH. The level may be elevated in many diseases, such as hepatitis and various cancers. The LDH level is often elevated in lymphoma and lymphocytic leukemias. Changes in the LDH level are nonspecific, but when LDH is elevated in the presence of lymphocytic cancers, the change may reflect the extent of the tumor and the rate of tumor growth. Lactate dehydrogenase monitoring is used in some cases, along with other measures, to plan the intensity of therapy for lymphoma. Also known as "lactic acid dehydrogenase."

Leukocytes. See White Blood Cells.

Lymphatic System. The system comprising the lymph nodes, the thymus gland (in the first several decades of life), the lymphatic channels, the lymphatic tissue of the marrow, the gastrointestinal tract, the skin and the spleen, as well as the T, B and natural killer (NK) lymphocytes contained in these sites.

Lymph Nodes. Bean-sized structures that contain large numbers of lymphocytes and are connected with each other by small channels

called “lymphatics.” These nodes are distributed throughout the body. In patients with lymphoma and some types of lymphocytic leukemia, the malignant lymphocytes multiply and the lymph nodes may become enlarged. This enlargement of lymph nodes can be seen or felt during physical examination, or measured by computed tomography (CT) scan or magnetic resonance imaging (MRI), depending on the degree of enlargement and the location.

Lymphocyte. A type of white blood cell that is essential to the body’s immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Macrophage. See Monocyte/Macrophage.

Magnetic Resonance Imaging (MRI). A technique that provides detailed images of body structures. It differs from the computed tomography (CT) scan in that the patient is not exposed to x-rays. Signals are generated in the tissues in response to a magnetic field produced by a specialized instrument and are converted by computer software into images of body structures. Healthcare professionals use MRI to measure either the size, or a change in size, of organs such as the lymph nodes, liver and spleen or tumor masses.

Marrow. See Bone Marrow.

Meninges. See Intrathecal.

Microarray. A laboratory tool used to analyze large numbers of genes or proteins at one time. In a microarray, biologic molecules such as DNA (deoxyribonucleic acid), RNA (ribonucleic acid), or protein are placed in a pattern onto a surface such as a glass slide. Other substances are added to these slides to detect specific patterns of molecules. Microarrays are being used to help diagnose diseases, such as cancer, and to develop treatments for them. See Gene Expression Profiling.

Monoclonal. See Clonal.

Monoclonal Antibody Therapy. See Immunotherapy.

Monocyte/Macrophage. A type of white blood cell that accounts for about 5 to 10 percent of the cells in normal human blood. The monocyte and the neutrophil are the two major microbe-eating and

microbe-killing cells in the blood. When monocytes leave the blood and enter tissues, they are converted into macrophages. The macrophage is the monocyte-in-action: It can combat infection in the tissues, ingest dead cells (in this function it is called a “scavenger cell”) and assist lymphocytes in their immune functions.

MRI. See Magnetic Resonance Imaging.

Mutation. An alteration in a gene that results from a change to a part of the stretch of DNA (deoxyribonucleic acid) that represents the gene. A “germ cell mutation” is a mutation that is present in the egg or the sperm and can be transmitted from parent to offspring. A “somatic mutation” is a mutation that occurs in a specific tissue cell and can result in the growth of that cell into a tumor. Most cancers start after a somatic mutation occurs. In leukemia, lymphoma or myeloma, undeveloped marrow (blood-forming) or lymph node cells undergo one or more somatic mutations that lead to the formation of a tumor. If a mutation results from a major chromosome abnormality, such as a translocation, it can be detected by cytogenetic analysis. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the oncogene (cancer-causing gene).

Neutropenia. An abnormally low concentration of neutrophils, a type of white blood cell.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. The neutrophil is the main cell that combats infections. Patients with certain blood cancers or who have undergone chemotherapy often do not have sufficient quantities of neutrophils circulating in their bloodstream. A severe deficiency of neutrophils increases the patient’s susceptibility to infection.

Nonmyeloablative Stem Cell Transplantation. See Reduced-Intensity Stem Cell Transplantation.

Oncologist. A doctor who diagnoses and treats patients with cancer. Oncologists are usually internists who undergo additional specialized training to treat adults (or pediatricians, to treat children) who have cancer. Radiation oncologists specialize in the use of radiation to treat cancer, and surgical oncologists specialize in the use of surgical procedures to diagnose and treat cancer. These doctors cooperate and collaborate to provide the best treatment plan for the patient, consisting of surgery, radiation therapy, chemotherapy and/or immunotherapy.

Pathologist. A doctor who identifies diseases by studying tissues under a microscope. A hematopathologist is a type of pathologist who studies diseases of blood cells by examining blood, bone marrow, lymph node and other tissue samples, and uses his or her expertise to identify diseases such as lymphoma. A hematopathologist uses a microscope to examine specimens and tissue and reviews the laboratory values, flow cytometry and molecular diagnostic test results to make the most accurate diagnosis. The hematopathologist works closely with the patient's hematologist-oncologist and based upon the diagnosis, will decide on the best treatment for the patient.

Phagocytes. Cells that protect the body from infection by eating and killing microorganisms, such as bacteria and fungi. The two principal phagocytes are neutrophils and monocytes. These cells leave the blood and enter tissues in which an infection has developed. Chemotherapy and radiation therapy can cause a severe decrease in the concentrations of these cells, which makes patients more susceptible to infection. Cancer treatment may suppress blood cell production in the marrow, resulting in lower numbers of these phagocytic cells.

Platelets. Small blood cells (about one-tenth the volume of red blood cells) that stick to the site of blood vessel injury, aggregate and then seal off the injured blood vessel to stop bleeding. "Thrombocyte" is a synonym for platelet and is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia (too few) or thrombocythemia (too many).

Positron Emission Tomography (PET) Scan. A procedure used to obtain images of lymphoma masses. In this technique, glucose (a type of sugar) is labeled with a positron particle that emits a radioisotope, such as fluorine-18. The utilization of sugar is greater in lymphoma cells than in normal tissue, so the isotope becomes concentrated in areas where lymphoma is present. The location of lymphoma sites in the body can be identified by scanning for intense positron particle emission. This technique is combined with computed tomography (CT) to establish the precise location of lymphoma masses, a procedure called PET-CT. Compared to other imaging procedures, PET can detect much smaller lymphoma masses. In some cases, successfully treated lymphoma masses may convert to fibrous tissue that still looks like a mass in imaging studies, perhaps leading the doctor to think that the mass was not successfully treated. Since lymphoma tissue is not fibrous and scars, which are primarily fibrous, do not absorb the fluorine-18-labeled sugar, PET scans can distinguish residual lymphoma masses from healed

scar tissue. Positron emission tomography is increasingly used for both staging of lymphoma and assessing response.

Radiation Therapy. The use of x-rays and other forms of radiation in cancer treatment. Radiation therapy may be useful in the treatment of localized lymphoma masses. Few cases of non-Hodgkin lymphoma are treated solely with radiation therapy because lymphoma cells are likely to be spread widely throughout the body. Radiation therapy can be an important addition to therapy when there are particularly large masses of lymphoma in a localized area, or when enlarged lymph nodes are compressing or invading normal organs or structures and chemotherapy cannot control the problem.

Radioimmunotherapy. See Immunotherapy.

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

Red Blood Cells. Blood cells that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. The red blood cells make up about 40 to 45 percent of the volume of the blood in healthy individuals. Also called “erythrocytes.”

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation. In reduced-intensity transplantation (also called “nonmyeloablative stem cell transplantation”), patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. **For more information about all types of stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Remission. The disappearance of evidence of a disease, usually as a result of treatment. The terms “complete” and “partial” are used to modify the term “remission.” Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is markedly improved by treatment, but residual evidence of the disease is present. A complete remission is usually required to achieve long-term benefits from treatment, especially in progressive lymphomas.

Serum. See Lactate Dehydrogenase (LDH).

Solitary Extranodal Lymphoma. See Extranodal Lymphoma.

Spleen. An organ located in the left upper portion of the abdomen, just under the left side of the diaphragm. It contains clusters of lymphocytes

and also filters old or worn-out cells from the blood. It is often affected in lymphocytic leukemias and lymphomas. Enlargement of the spleen is called “splenomegaly.” Surgical removal of the spleen is known as “splenectomy.”

Stem Cells. Immature (undeveloped) cells in the bone marrow that are essential to the formation of red blood cells, white blood cells and platelets. They are primarily found in the marrow, but some leave the marrow and circulate in the bloodstream. Using special techniques, the stem cells in blood can be collected, preserved by freezing and later thawed and used for stem cell therapy. See Hematopoiesis.

Thrombocytopenia. An abnormally low concentration of platelets in the blood.

Thymus. A lymphoid organ located immediately beneath the breastbone at the level of the heart. The thymus serves a vital role in the formation and development of T lymphocytes (T cells). The human thymus becomes much smaller as puberty approaches.

Toxin. A naturally derived substance that is poisonous to cells. A toxin can bind to antibodies that then attach to cancer cells. The toxin may kill the cancer cells.

Translocation. An abnormality of chromosomes in marrow or lymph node cells that occurs when a piece of one chromosome breaks off and attaches to the end of another chromosome. In a balanced translocation, genetic material is exchanged between two different chromosomes with no gain or loss of genetic information. When a translocation takes place, the gene at which the break occurs is altered. This is one form of somatic mutation that may transform the gene into an oncogene (cancer-causing gene). See Mutation.

White Blood Cells. Any of the five major types of infection-fighting white blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. Also called “leukocytes.”

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