LEUKEMIA & LYMPHOMA SOCIETY®

Non-Hodgkin Lymphoma

Tom, non-Hodgkin lymphoma survivor

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Revised **2018**

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

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

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

- **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**

Inside This Booklet

Acknowledgement

The Leukemia & Lymphoma Society appreciates the review of this material by

James O. Armitage, MD
The Joe Shapiro Professor of Medicine
Division of Oncology/Hematology
University of Nebraska Medical Center
Omaha, NE

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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 start in the lymphatic system. Brief descriptions of normal blood and bone marrow, the lymphatic system, and definitions of medical terms are included in this booklet.

An estimated 653,653 people in the United States are either living with or in remission from NHL. About 74,680 people were expected to be diagnosed with NHL in 2018 (see *Incidence, Causes and Risk Factors* on page 46). Advances in the treatment of NHL are resulting in improved remission and cure rates. New approaches to therapy 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, which is 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. A discussion of NHL subtype treatments begins on page 20.

You can find more information about Hodgkin lymphoma in the free LLS booklet *Hodgkin Lymphoma*.

About Non-Hodgkin Lymphoma

"Non-Hodgkin lymphoma (NHL)" is the term that encompasses 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 our immune system. They can be either B cells, T cells or natural killer (NK) cells. In lymphoma, a lymphocyte undergoes a malignant (cancerous) change and 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 the bone marrow (the spongy tissue in the hollow central cavity of the bones that is the

site of blood cell formation) and blood. 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. They are designated either "lymphoblastic" or "lymphocytic" leukemias. Lymphomas begin when a cell undergoes a change (mutation) in a lymph node or in some other lymphatic structure. Lymphomas are found in the skin, the gastrointestinal tract, or other sites in the body. It is important to recognize that leukemias, which originate in the 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 REAL/WHO (The Revised European American Lymphoma [REAL] and World Health Organization [WHO] classification of non-Hodgkin lymphoma [NHL]) classification 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. A hematopathologist, a doctor who specializes in the diagnosis of blood disorders and blood cancers, should review biopsy samples since the prognosis and the approach to treatment are influenced by the study of diseased cells and tissues viewed under a microscope (histopathology).

One way that NHL subtypes are designated is by cell type. Some NHL subtypes involve lymphocytes called "B cells" (eg, diffuse large B-cell lymphoma (DLCBL) and follicular lymphoma [FL]). Other subtypes involve lymphocytes called "T cells" or "natural killer (NK) cells" (eg, peripheral T-cell lymphoma and cutaneous T-cell lymphoma). Specialists further characterize the NHL subtypes according to the rate at which the disease progresses. The progression may be 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 represent about 40 percent of all NHL cases. Follicular lymphoma is the most common subtype of indolent NHL. When indolent lymphomas are first diagnosed, patients have fewer signs and symptoms than patients with aggressive lymphoma subtypes. Some cases of indolent NHL transform into aggressive NHL. The subtype (either aggressive or indolent) that is diagnosed determines the appropriate treatment; so, getting an accurate diagnosis is very important.

Table 1, on page 4, provides a list of some of the NHL subtypes designated as either aggressive or indolent. Table 2, on page 5, lists some of the diagnostic designations for NHL subtypes, based on the WHO classification.

There are many concerns, questions and considerations when you are diagnosed with non-Hodgkin lymphoma. Before treatment begins, raise any questions you have about treatment planning and issues such as fertility and other possible long-term and late effects with your doctor and the members of your healthcare team. Be sure you understand the doctor's responses, discuss your concerns, and explore any issues you encounter.

The information in this booklet covers many NHL subtypes and provides detailed information (including diagnosis, staging and treatment) about the more common ones. It also provides a brief description of normal blood, bone marrow, and the lymphatic system, as well as a list of health terms that will help readers understand information that may be new to them.

Most Common Subtypes of Non-Hodgkin Lymphoma (NHL)

Aggressive Subtypes

Rapidly progressing or high-grade NHL subtypes represent about 60% of all NHL cases. Diffuse large B-cell lymphoma is the most common aggressive subtype.

- Anaplastic large-cell lymphoma
- Acquired immune deficiency syndrome (AIDS)-associated lymphoma
- Burkitt lymphoma
- Central nervous system lymphoma
- Diffuse large B-cell lymphoma
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Peripheral T-cell lymphoma
- Transformed follicular and transformed mucosa-associated lymphoid tissue (MALT) lymphomas

Indolent Subtypes

Slow-growing or indolent subtypes represent about 40% of all NHL cases. Follicular lymphoma is the most common subtype of indolent NHL.

- Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)
- Follicular lymphoma
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
- Marginal zone B-cell lymphoma
- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
- Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma

Table 1. Some of the most common indolent and aggressive NHL subtypes are listed in this table. Some cases of indolent NHL transform into aggressive NHL.

Diagnostic Designations for Non-Hodgkin Lymphoma (NHL)

NHL Subtypes

Mature B-cell lymphomas

- Chronic lymphocytic leukemia/small-cell lymphocytic lymphoma
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Marginal zone lymphoma
  - Nodal marginal zone lymphoma
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
  - Extragastric MALT lymphoma
  - Splenic marginal zone lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
  - High-grade B-cell lymphoma with double or triple hits
  - Primary cutaneous DLBCL, leg type
  - Primary DLBCL of the central nervous system
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma unclassifiable

Mature T-cell and natural killer (NK)-cell lymphomas

- Peripheral T-cell lymphoma
  - Hepatosplenic gamma/delta T-cell lymphoma
  - Subcutaneous paniculitis-like T-cell lymphoma
  - Enteropathy-associated T-cell lymphoma
- Cutaneous T-cell lymphoma
  - Mycosis fungoides
  - Sézary syndrome
- Angioimmunoblastic T-cell lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal T-/NK-cell lymphoma, nasal type
- Anaplastic large-cell lymphoma
  - Primary cutaneous anaplastic large-cell lymphoma
  - Systemic anaplastic large-cell lymphoma

Table 2. 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) in some disease subtypes refer to the specific areas of normal lymph nodes (the follicle, mantle and marginal zones) where the lymphoma originated.

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. The doctor will order additional tests and a tissue biopsy to make a diagnosis (see *Diagnosis* on page 8). The signs and symptoms of NHL are also associated with a number of other, less serious diseases.

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).

- Most patients with NHL have one or more enlarged lymph nodes in the neck, armpit or groin.
- Less often, 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 the lymph nodes, 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 (see Figure 1 on page 7).

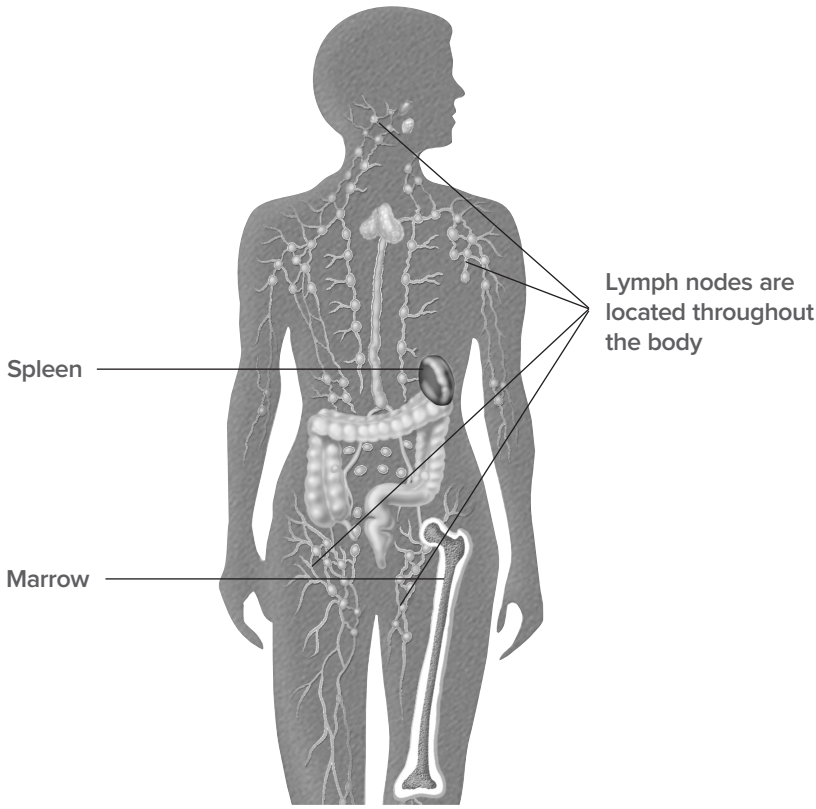
Common Symptoms. These include

- 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 symptoms and the disease may be discovered during a routine medical examination or while the patient is under care for an unrelated condition.

B Symptoms. Fever, drenching night sweats and loss of more than 10 percent of body weight over 6 months are sometimes termed "B symptoms." 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. Further, they are not considered to be B symptoms.

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.

Figure 1. 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 grow, 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.

Evaluation. The doctor will take a comprehensive medical history and ask questions regarding either the absence or the 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.

A diagnosis of NHL is usually made by microscopic examination of a lymph node biopsy specimen (a piece of lymph node obtained from a biopsy). This examination includes tests called "immunophenotyping" and "cytogenetic analysis." More information about these tests is found on page 9. 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 and the name of the subtype for them.

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 that is used to obtain a sample of lymph node tissue). Then the hematopathologist will examine the tissue under the microscope and analyze the findings. If there is any doubt about the diagnosis, or to confirm it (in the case of a rarer 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 the subtype. A needle biopsy (a fine-needle aspiration [FNA]) may be done, but the specimen of the lymph node tissue that can be obtained through a needle is usually not sufficient for the hematopathologist to make a firm 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 which type of biopsy to use is based on the location of the tumor. Tissue can generally be removed after the patient is given a local anesthetic.

The tissue specimen 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 provide confirmation that a person has lymphoma as well as identification of the type of lymphoma. Sometimes, hematopathologists can determine a person's

NHL subtype by looking at the cells from the tissue specimen. 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 the lung or bone. When lymphoma is detected exclusively outside of the lymph nodes, it is called "primary extranodal lymphoma," and the biopsy specimen 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 order to identify NHL cells and confirm a diagnosis. Immunophenotyping can further help determine whether the lymphoma cells are B cells, T cells or natural killer (NK) cells. The pattern of protein expression can provide important information on the biology of the lymphoma.
- Flow cytometry—Similar to immunophenotyping, this technique takes cells from the blood or tissue biopsy and sends them through a machine that will detect which proteins or markers (antigens) are expressed in the lymphoma cells.
- Cytogenetic analysis—Dividing cells are studied to see if any chromosomal abnormalities are present. Fluorescent in situ hybridization (FISH) is a type of laboratory test that uses special dyes to look for 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 identify cancer subtypes and risk factors. The test findings help doctors to predict how patients will respond to treatment, as well as which patients may be at increased risk for disease relapse. For example, gene expression profiling is used to identify different forms of diffuse large B-cell lymphoma. However, gene expression profiling and microarray analysis are not generally used in clinical practice and these tests are still mostly used as research tools.
- Polymerase chain reaction (PCR)—A technique to expand trace amounts of DNA (deoxyribonucleic acid) and/or RNA (ribonucleic acid) so that the specific type of the DNA and/or RNA can be determined. This method has become useful in detecting a very low concentration of residual lymphoma cells—too few to be seen by using a microscope. The technique can detect the presence of one lymphoma cell among 500,000 to 1 million healthy cells. This test is a possible predictor of how well a patient will respond to treatment with specific therapies. The use of PCR requires that a specific DNA abnormality or marker, such as an oncogene, is present in the lymphoma cells.

Staging

Doctors use physical examinations, imaging and laboratory test findings to discover the extent of the disease. The doctor needs this information to determine the "stage" of the disease" (see Table 3 on page 13 and Figure 3 on page 14). Staging is a very important part of treatment planning.

Imaging Tests. The physical examination and imaging tests help the doctor 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 site or another.

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 tissue.

The imaging tests may include

- Chest x-rays
- A CT (computed tomography) 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 an image that shows a cross section of the area being examined. Patients have 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.
- An FDG-PET (fluorodeoxyglucose[FDG]-positron emission tomography [PET]) scan—A PET scan is an imaging technique that produces a 3D image of functional processes in the body. In an FDG-PET scan a small amount of a radioactive sugar called "fluorodeoxyglucose (FDG)" is used to show differences between healthy and nonhealthy tissue. A small amount of FDG is injected into the patient. Cancer grows at a faster rate than healthy tissue, so cancer cells absorb more of the radioactive FDG. 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.

- Magnetic resonance imaging (MRI)—Magnetic resonance imaging is used in select cases. MRI 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 saved on a disk for future analysis.
- Positron emission tomography-computed tomography (PET-CT) scans—This procedure combines the techniques of both PET and CT imaging. Both tests are done at the same time and in the same machine. 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.

  PET scans are increasingly being used not only to stage the disease precisely, but also to determine the margins of radiotherapy (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 functions; and measure important biological markers, which are helpful prognostic indicators for several NHL subtypes.

Some of the blood tests used to determine the need for treatment and the extent of disease include

- Complete blood count (CBC)—This test measures different components of the blood. Test results include counts of red blood cells, white blood cells and platelets. A CBC may show
  - Anemia (low red blood cell counts)
  - Neutropenia (a low neutrophil [a type of white blood cell] count)
  - Thrombocytopenia (a low platelet count).
- Comprehensive metabolic panel—This panel often includes tests for up to 14 chemicals. Chemicals in the blood come from the liver, bone and other organs. Abnormal levels can be caused by cancer or other health problems.
- $Beta_2$ microglobulin—$Beta_2$ microglobulin is a small 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.
- Lactate dehydrogenase (LDH)—LDH is a protein that is 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—This test measures the amount of uric acid in the body. When cancer cells breakdown and die, they release substances into the blood. If the cancer cells breakdown too quickly, the kidney's 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 42.
- Antibody testing—Antibodies or 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 levels of antibodies or very high amounts of tumor-specific antibodies. The "quantitative immunoglobulins" test measures the amount of each type of antibody. The "serum protein electrophoresis (SPEP)" test measures the amount of specific monoclonal antibodies in the blood.

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

Heart Tests. Some cancer treatments can damage the heart. So, members of the treatment team may want to determine how well a patient's heart functions before he or she starts a specific treatment. 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 associated with a specific subtype and are not necessary for all patients with NHL. Examples of specific testing include a

- Full evaluation of the gastrointestinal (GI) tract, including upper and lower endoscopies for patients who have disease involving the GI tract, such as mantle cell lymphoma (MCL) and gastric mucosa-associated lymphoid tissue (MALT) lymphoma
- Colonoscopy for patients with MCL (routine colonoscopy is important for all persons 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 may be required for patients with certain subtypes or symptoms that suggest central nervous system involvement.

Stages of Non-Hodgkin Lymphoma (NHL) with Categories

Stage I

- I: Involvement of one lymph node region (for example, the tonsils)
- IE: Involvement of one organ or area outside the lymph nodes

Stage II

- II: Involvement of two or more lymph node regions and both are either above or below the diaphragm
- IIE: Involvement of one or more lymph node groups 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

Stage III

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

Stage IV

- Involvement of one of more organs that area 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 of 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 extends to an area or organ beyond the lymphatic system
- **S—** "S" stands for spleen and it means the lymphoma is found in this organ
- **X —** "X" indicates "bulky disease." This is a nodal mass whose greatest size is usually more than 10 cm or more than one third of the chest diameter by x-ray.

Table 3. The stages and modifying features of NHL.

Keep in mind that "stage IV" does not have the same implications in NHL as it does for many other cancers. 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 does not reflect how well or how poorly a patient may respond to treatment. More than 50 percent of patients with aggressive disease and more than 80 percent of patients with indolent types of NHL are diagnosed either with stage III or even stage IV disease. Disease identified as stage IV NHL may be highly treatable, depending on the patient's specific subtype of disease.

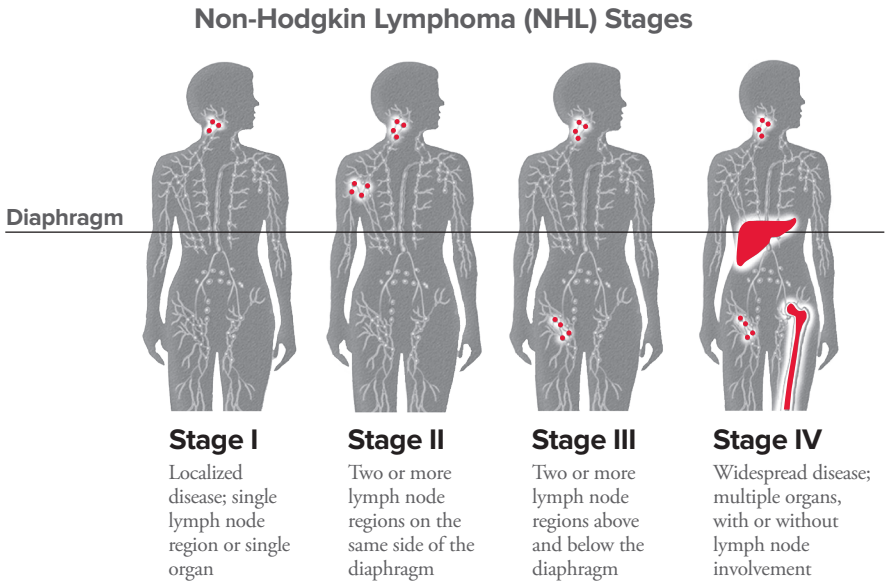


Figure 3. This illustration shows the location of non-Hodgkin lymphoma in the body for each stage.

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

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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 disease is eliminated. Patients who go into remission are sometimes cured of their disease. Treatment can also keep non-Hodgkin lymphoma (NHL) in check for many years, even though imaging or other studies show remaining sites of disease. This situation may be referred to as a "partial remission."

For patients without symptoms and with indolent subtypes of NHL, the treatment may be the watch-and-wait approach, meaning 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. Some patients have a long-time slow-growing disease, while others have a disease that evolves (transforms) into a more aggressive type of NHL that requires immediate treatment.

In general, chemotherapy (see Table 4 and Table 5, on pages 16 and 17) and radiation therapy are the two principal forms of treatment for NHL. Although radiation therapy is often neither the sole nor the principal curative therapy, it is an important additional treatment in some cases.

Stem cell transplantation may also be used to treat some NHL subtypes. You can see more information on stem cell transplantation on page 37 and in the free LLS booklet *Blood and Marrow Stem Cell Transplantation*. Other forms of treatment are emerging, and some are already approved for specific subtypes of NHL. Many other new therapies are being developed in clinical trials.

Table 5 on page 17 contains examples of drug combinations that are used to treat NHL. Researchers in clinical trials continue to study the most effective combinations of drugs for the treatment of all types of NHL including newly diagnosed, refractory or relapsed cases.

Some Drugs Used in the Treatment of Non-Hodgkin Lymphoma (NHL)

Alkylating (DNA-Damaging) Drugs

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

Antifolate

- Pralatrexate (Folotyn®)

Antitumor Antibiotics

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

Antimetabolites

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

Proteasome Inhibitor

- Bortezomib (Velcade®)

DNA Repair Enzyme Inhibitors

- 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

Immunotherapy

- Alemtuzumab (Campath®)
- Axicabtagene ciloleucel (Yescarta™)
- Brentuximab vedotin (Adcetris®)
- Obinutuzumab (Gazyva®)
- Ofatumumab (Arzerra®)
- Rituximab (Rituxan®)
- Rituximab + hyaluronidase human (Rituxan Hycela™)
- Yttrium-90+ ibritumomab tiuxetan (Zevalin®)

Bruton Tyrosine Kinase (BTK) Inhibitors

- Acalabrutinib (Calquence®)
- Ibrutinib (Imbruvica®)

Histone Deacetylase Inhibitors (HDAC)

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

PI3K Inhibitors

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

Retinoid

- Bexarotene (Targretin®)

Table 4. This table includes the drugs that are being used to treat different subtypes of NHL.

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

Some Drug Combinations Used to Treat Non-Hodgkin Lymphoma (NHL)

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

R-CHOP: Rituximab (Rituxan®) plus (cyclophosphamide [Cytoxan®], 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®), cisplatin (Platinol®)

ICE: Ifosfamide, carboplatin, etoposide

m-BACOD: Methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone

MACOP-B: Methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone plus bleomycin

ProMACE CytaBOM: Prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate

CNOP: Cyclophosphamide, mitoxantrone, vincristine, prednisone

Table 5. Clinical trials continue to study the most effective combinations of drugs for the treatment of all types of NHL (newly diagnosed, refractory or relapsed).

Factors That Influence Treatment. Each person should discuss treatment options with his or her doctor and ask for help understanding the benefits and risks of different treatment approaches. The most effective treatment plan for a patient with NHL is individualized and depends on

- The subtype of NHL (knowing whether the lymphoma cells are most closely 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 forming decisions about treatment (see Table 3 on page 13)
- Factors, such as fever, drenching night sweats and loss of more than 10 percent of body weight over 6 months, referred to as "B symptoms"

- The presence of 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 for most patients. However, medical problems, including the patient's overall health status, and the patient's decisions about treatment are significant considerations. When making treatment decisions, it is important to include a discussion about fertility and long-term and late effects.

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 NHL, it identifies several unfavorable prognostic factors.

The IPI is calculated for all patients (a score of 0-5) and for patients aged 60 years or younger (a score of 0-3) by totaling the sum of the points scored for each of the following risk factors.

Risk factors in all patients (one point is assigned for each factor)

- Older than 60 years
- Serum lactate dehydrogenase (LDH) concentrations higher than the highest normal value
- Eastern Cooperative Oncology Group (ECOG) performance status
- Stage III or IV disease
- Extranodal involvement in two or more sites.

Risk factors in patients 60 years of age or younger (one point is assigned for each factor).

- Serum LDH concentrations higher than the highest normal value
- The ECOG performance status
- Stage III or IV disease.

The ECOG performance status is a scale used to evaluate a person's ability to perform daily tasks of living without help.

The IPI index helps doctors predict overall survival and the risk of relapse, and provide a basis for recommending either more or less aggressive treatment for high-risk patients.

The number of IPI risk factors a person has defines the corresponding IPI risk group to help predict the risk of relapse. Each point represents some increased risk for disease relapse. The total number of points identifies the following risk groups:

- 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 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 doctor in order to understand treatment options, including participation in clinical trials.

Pretreatment Considerations. Adults of childbearing age and parents of children diagnosed with NHL should ask their doctor 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,* page 45). For more information, see the free LLS booklets *Fertility* Facts *Long-Term and Late Effects of Treatment in Adults* Facts and *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma* Facts).

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

Short periods of hospitalization are sometimes required. Particularly intensive therapy 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, see the free LLS booklet *Blood Transfusion*.

Treatment Considerations for Children, Adolescents and Young Adults. Non-Hodgkin lymphoma accounts for an estimated 5 percent of cancers in children younger than 15 years. Burkitt lymphoma is the predominant NHL subtype in children aged 5 through 14 years.

Children and adolescents with NHL should be referred to medical centers that have a specialized pediatric oncology team to ensure that young patients 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 the specific subtype of NHL. Doctors use this information about the patient's disease in order to determine the most effective therapy. It is also important to discuss the planned therapy with members of the oncology team to learn about the drugs, potential side effects and long-term effects, including fertility and the treatment schedule. See *Pretreatment Considerations,* on page 19.

Different treatment strategies may be used for children and for adults with NHL. The choice of therapy for adolescents and young adults can be challenging and it is a topic of ongoing research. Pediatric treatment strategies are used to treat 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 setting or with a pediatric protocol as part of a clinical trial. With current treatments, NHL in most children is highly curable. 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. For more information, see the free LLS booklet *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma* Facts.

Treatment of Aggressive Subtypes

Every patient's situation should be evaluated individually by an oncologist who specializes in treating non-Hodgkin lymphoma (NHL) and who will discuss the disease subtype, stage and treatment options with the patient. It is also important to seek 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 frequently treated with chemotherapy that consists of four or more drugs. In most cases this is the combination therapy called **R-CHOP** (rituximab [Rituxan®] plus cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone).

This intensive, multidrug chemotherapy can be very effective for aggressive lymphoma, 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 and represents about 30 percent of cases of NHL diagnosed in the United States. Diffuse large B-cell lymphoma is a cancer of B cells (lymphocytes). Some subtypes of DLBCL start from B cells found within the germinal centers inside lymphatic organs. Germinal centers are short-lived structures that are formed in response to an outside antigen. B cells experience changes within the germinal center in preparation to make antibodies. Other subtypes of DLBCL start from 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 the initial diagnosis. For other patients, an indolent lymphoma, such as a small-cell lymphocytic lymphoma or a follicular lymphoma, transforms and becomes a DLBCL. Although DLBCL can occur at any age, it most commonly is found in middle-aged and older persons. Most cases have no known cause.

Gene expression profiling (see page 60) has been used to define groups of patients; one group of patients may have different responses to therapy, another group may have a different clinical presentation that is 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. They are

- Germinal center B-cell-like (GCB)
- Nongerminal center B-cell-like (non-GCB)
- Primary mediastinal B-cell lymphoma (PMBL).

These distinct DLBCL subtypes arise due to specific genetic changes. Because gene expression profiling is not commercially available, most oncologists, working with

hematopathologists, will perform immunophenotyping to identify the specific proteins that are associated with either the GCB or the non-GCB subtype of DLBCL.

According to some studies, DLBCL patients who appear to have the GCB subtype experience significantly better treatment outcomes than patients who do not have the GCB subtype. A number of clinical trials are under way to investigate whether using novel approaches to therapy improves treatment outcomes for non-GCB DLBCL patients. Primary mediastinal B-cell lymphoma (PMBL) is a subtype of DLBCL that is marked by the overgrowth of scarlike lymph tissue. A tumor generally forms behind the breastbone and may cause coughing and difficult breathing. The tumor is often very large and can cause pressure on the blood vessels or the heart and lungs. It occurs in young adults around age 35 and it affects slightly more women than men.

Rituximab (Rituxan®) is indicated for previously untreated DLBCL; cluster designation (CD) 20-positive NHL in combination with **CHOP** or other anthracycline-based chemotherapy regimens. Diffuse large B-cell lymphoma is frequently treated with a chemotherapy regimen that is made up of four or more drugs known as **R-CHOP** (rituximab [Rituxan®], cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone). This combination 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 patients.

Patients with PMBL often need more intense treatment than other patients with DLBCL. The chemotherapy combination, R-CHOP, is the standard regimen used for PMBL; however, R-CHOP is increasingly being replaced by more intense regimens, including **dose adjusted EPOCH-R**, which comprises dose-adjusted etoposide, prednisone, vincristine (Oncovin®), cyclophosphamide, hydroxydoxorubicin (doxorubicin) plus rituximab.

The combination of the monoclonal antibody rituximab and an endoglycosidase known as **"hyaluronidase human"** (Rituxan Hycela™) is approved by the Food and Drug Administration (FDA) 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.

Relapsed DLBCL. About 30 to 40 percent of patients relapse after their first chemotherapy treatment. For these patients, additional chemotherapy (called "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.

Axicabtagene ciloleucel (Yescarta™), an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, is approved by the FDA for the treatment of adult patients with either 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. Yescarta is not indicated for the treatment of patients who have primary central nervous system (CNS) lymphoma.

Tisagenlecleucel (Kymriah™), a CD19-directed genetically modified autologous T-cell immunotherapy, is 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. Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

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

"Double-hit" and "triple-hit" lymphoma. The 2016 revision of the World Health Organization (WHO) classification for lymphoma (see Table 2 on page 5) 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* or *BCL6* genes. "Double-hit" is the term used to describe a lymphoma in which the malignant cells exhibit mutations on two significant genes. Double-hit lymphoma has been observed in 2 to 11 percent of newly diagnosed patients with DLBCL. These patients have rearrangements (mutations) of the *MYC* gene and either a *BCL2* or a *BCL6* gene rearrangement. When all three rearrangements are present, the cancer is called a "triple-hit" lymphoma. These lymphoma subtypes respond poorly to the standard **R-CHOP** therapy, have an increased risk of 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 DLCBLs without double-hit or double expression. The treatment of double-hit and triple-hit lymphoma has become the subject of ongoing clinical trials.

Peripheral T-Cell Lymphoma (PTCL). Peripheral T-cell lymphoma refers to a group of aggressive NHL subtypes that originate in T-cell lymphocytes. Very early forms of T cells, called "precursors," originate in the bone marrow. They travel from the marrow to the thymus to become mature T-cell lymphocytes. When they are ready to help fight illness, they leave the thymus and travel to other

lymph tissue, such as the lymph nodes. Peripheral T-cell lymphoma starts from T cells that have left the thymus, hence this is a cancer of mature T cells.

Peripheral T-cell lymphoma generally affects people aged 60 and older and it is diagnosed slightly more often in men than in women. However, younger adults and children are also sometimes diagnosed with PTCL. It is a rare disease in the United States. Some forms of PTCL are more common in Asia, Africa and the Caribbean, possibly as a result of exposure to specific viruses, such as the Epstein-Barr virus (EBV) and the human T-cell leukemia 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, named as such because it does not fit into any of the other PTCL classifications. It often involves lymph node sites, but other areas, such as the liver, bone marrow, GI tract and skin, can be involved.
- Anaplastic large-cell lymphoma (ALCL)—This subtype usually starts in lymph nodes and can spread to the skin. The cancer cells express the marker CD30 on the surface of the cells. There is a protein called "anaplastic lymphoma kinase (ALK1)" inside the lymphoma cells. The two main subtypes of ALCL are
  - Systemic ALCL (sALCL)
    - ALK1-positive—This subtype begins in the lymph nodes and the disease may spread to other parts of the body. About 80 percent of patients with this subtype are cured. This disease is more common in young people.
    - ALK1-negative—This subtype, which does not express the ALK1 protein, occurs mainly in older patients. Treatment with chemotherapy or radiation therapy is often less successful and a stem cell transplant may be discussed.
  - Primary cutaneous anaplastic large-cell lymphoma (pcALCL)—This subtype mostly affects the skin, but other parts of the body may be involved.
- Hepatosplenic T-cell lymphoma—This uncommon type of PTCL usually affects young men. It starts in the liver and spleen and these cancer cells have a receptor called "gamma/delta" on the surface of the cell.
- Angioimmunoblastic T-cell lymphoma—This type of T-cell lymphoma often involves lymph nodes and the bone marrow and is generally associated with viral infection. Many patients have "paraneoplastic symptoms" including fevers, rash and abnormal protein levels in their blood.
- Enteropathy-associated T-cell lymphoma (EATL)—This T-cell lymphoma 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. It is usually a very aggressive lymphoma that requires both chemotherapy and radiation. ENK/TCL is more common in people of Asian origin.

Peripheral T-cell lymphoma is one of the most difficult types of lymphoma to treat. It is commonly treated with the regimens that are used for DLBCL. Chemotherapy with **CHOP** (cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], vincristine [Oncovin®], and prednisone) is the standard treatment for newly diagnosed PTCL; however, the treatment outcomes are not as favorable as they are for DLBCL. Studies are under way to try to develop new treatment approaches, and patients are encouraged to seek out clinical trials.

While chemotherapy remains an important therapeutic option, four new drugs have been approved for the treatment of PTCL. They are

- **Pralatrexate** (Folotyn®), given by IV injection, is an antifolate drug and is FDA approved for the treatment of patients with relapsed or refractory PTCL.

- **Romidepsin** (Istodax®), given by IV infusion, a type of histone deacetylase (HDAC) inhibitor, is approved by the FDA for the treatment of PTCL patients who have received at least one prior therapy.

- **Brentuximab vedotin** (Adcetris®), given by IV infusion, is FDA approved for the treatment of patients with the PTCL subtype sALCL after failure of at least one prior multiagent chemotherapy regimen. It is also approved for the treatment of adult patients with pcALCL or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy. This drug is a type of conjugated monoclonal antibody, which targets CD30 and releases the chemotherapy drug MMAE into the cell.

- **Belinostat** (Beleodaq®), given by IV infusion, is an HDAC inhibitor that is FDA approved for the treatment of patients who have either relapsed or refractory PTCL.

In addition to these newly approved drugs, a number of novel therapeutic agents and regimens in several drug categories are under investigation. For more information about PTCL, including treatment options, see the free LLS booklet *Peripheral T-Cell Lymphoma* Facts.

Acquired Immunodeficiency Syndrome (AIDS)-Associated Lymphoma.

The types of NHL that are most often seen in people with AIDS are DLBCL, Burkitt lymphoma and primary 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 developing AIDS-associated NHL has decreased in the last several years because of improved human immunodeficiency virus (HIV) treatment.

Burkitt Lymphoma. This aggressive B-cell subtype grows and spreads very quickly and represents about 2.5 percent of NHL cases. It may involve the jaw, bones of the face, bowel, kidneys, ovaries, marrow, blood, CNS 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. They are

- Endemic Burkitt lymphoma—occurs commonly in Africa and is associated with the EBV
- Sporadic Burkitt lymphoma—occurs throughout the world
- Immunodeficiency-related Burkitt lymphoma—often seen in patients with AIDS.

Burkitt lymphoma may spread to the brain and spinal cord (part of the CNS), therefore, treatment to prevent CNS spread should be included in any treatment regimen. **CHOP** or **CHOP-like** chemotherapy does not produce favorable results. Instead, highly aggressive chemotherapy 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** (hyperfractionated 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 an 80 to 90 percent survival rate among adults with Burkitt lymphoma who are treated with the aggressive chemotherapy regimens listed. Patients who do not respond to an intensive regimen are encouraged to participate 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 who have primary CNS lymphoma in the United States do not have a clear predisposing cause. Secondary CNS lymphoma starts with lymphoma in other parts of the body and then spreads to the brain and/or the spinal cord. Patients with highly aggressive lymphomas, such as Burkitt lymphoma, DLBCL and

PTCL, are at a higher risk of CNS relapse. Thus, first-line treatment for these types of lymphoma may include chemotherapy given 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 just been diagnosed or has relapsed, and the patient's age and general health. Treatment may consist of standard therapy or treatment that is 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 for CNS lymphoma are being studied in clinical trials.

Mantle Cell Lymphoma (MCL). People with MCL represent about 6 percent of NHL cases. The malignant cells originate from a lymphocyte in the mantle zone of a lymph node. This subtype usually occurs in people over age 60 and is found more frequently in men than in women. The disease begins in the lymph nodes and spreads to the spleen, blood, bone marrow and sometimes the esophagus, stomach and intestines. Patients generally have stage III or IV disease at diagnosis.

Mantle cell lymphoma cells express too much of a protein called "cyclin-D1." Some patients do not show signs or symptoms of the disease, so delaying treatment may be an option for them. Most patients need to start treatment after diagnosis. Standard treatment is combination chemotherapy, either with or without an autologous stem cell transplant.

Common treatment regimens for this subtype of NHL include **CHOP** in which bortezomib (Velcade®) is used instead of vincristine; bendamustine plus rituximab; and various regimens including high-dose cytarabine.

Additional agents have received approval for relapsed/refractory disease. These are

- **Acalabrutinib** (Calquence®), given by mouth, is FDA approved for the treatment of adults with MCL who have received at least one prior therapy.
- **Bortezomib** (Velcade) is FDA approved to treat people with MCL. Bortezomib is approved for IV administration in MCL and for subcutaneous (injected under the skin) administration.
- **Ibrutinib** (Imbruvica®), given by mouth, is approved for patients who have received at least one prior therapy. Ibrutinib has been demonstrated to be a very well-tolerated drug with minimal toxicity.
- **Lenalidomide** (Revlimid®), given by mouth, is approved for patients whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

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

Angioimmunoblastic Lymphoma. Patients with this diagnosis are treated in the same way as patients with acute lymphoblastic leukemia (ALL). Diagnosis and treatment of ALL is described in detail in the free LLS booklet *Acute Lymphoblastic Leukemia.*

Approaches to Therapy for Advanced-stage Aggressive NHL Subtypes. The standard of care for advanced-stage disease is **R-CHOP** (rituximab [Rituxan®] plus cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone).

The number of chemotherapy cycles used depends upon the stage and extent of disease. If the lymphoma is in the bone marrow, nasal sinuses or testicles, or if it is near the spinal cord, it may spread to the CNS. Therefore, chemotherapy may be given into the spinal fluid.

Patients with high-risk disease based on prognostic factors may benefit from more aggressive initial treatment and should discuss clinical-trial options with their doctors.

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 for any given patient is highly individual and depends on factors that include the patient's

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

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

For early-stage disease

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

For advanced-stage disease

- The watch-and-wait approach for asymptomatic patients
- Monoclonal antibodies (**rituximab, obinutuzumab** [Gazyva], **yttrium-90+ibritumomab 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) an active form of therapy, involving careful monitoring and follow-up care. Patients need to discuss with their doctors the potential benefits of the watch-and-wait approach versus initiating chemotherapy and/or other therapies. Studies comparing the watch-and-wait approach to initial therapy have shown no survival advantage in the group of patients who were treated at diagnosis compared to survival of patients who were observed. Studies are ongoing, and one trial showed that when the watch-and-wait approach and treatment with rituximab (Rituxan®) were compared, the rituximab treatment increased the time until a patient needed chemotherapy. However, no major difference in quality of life was observed, and the overall survival was the same. More studies need to be done to confirm this data.

There are some patients with indolent lymphoma who need aggressive initial therapy. However, patients with no symptoms and limited extent of disease frequently can 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. Therapy should be started for a patient who 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 red blood cell, low white blood cell or low platelet counts. The specific decision to treat indolent lymphoma is made collaboratively by the oncologist and patient. Each case is evaluated individually and approaches vary among patients.

Follicular Lymphoma (FL). This is the second most frequently occurring type of NHL, accounting for about 22 percent of 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, *BCL-2*, and makes the cells resistant to therapy. Some FLs have a deletion of the short arm of chromosome 1 (1p36). These lymphomas grow throughout tissue rather than in clusters. They also express cluster designation (CD) 23 (CD23). These lymphomas are usually found within the inguinal (groin) nodes.

Follicular lymphoma is a very slow-growing disease. Some patients may not need treatment for several years, whereas others may have extensive lymph node or organ

involvement and need treatment right away. Most patients with FL are aged 50 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; patients with less advanced disease can be observed with periodic examinations and imaging tests.
- Radiation therapy
- Chemotherapy with **rituximab** followed by radiation therapy.

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

For patients with stage II FL who have large lymph nodes, stage III or stage IV FL, or advanced-stage relapsed FL, treatment will be based on symptoms, the patient's age and health status, the extent of disease and the patient's choice. A patient who requires 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)**
  - Single chemotherapy drugs in combination with **rituximab**. Examples of drugs used for treatment include **cyclophosphamide**, **chlorambucil** or **bendamustine hydrochloride** (Bendeka®)
  - Chemotherapy combinations plus rituximab, such as **R-CVP** (rituximab plus cyclophosphamide [Cytoxan®], hydroxydoxorubicin [doxorubicin], vincristine [Oncovin®] and prednisone) or **R-CHOP** (rituximab [Rituxan®] plus cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone)
  - Maintenance **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). Rituximab maintenance may be continued for 2 years.
- Autologous and allogeneic stem cell transplantation for selected patients
- Targeted therapy, using kinase inhibitors

- **Idelalisib** (Zydelig®), a PI3K kinase inhibitor given by mouth, which is FDA approved 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 IV infusion, is approved as therapy for adult patients with relapsed FL who have received at least two prior systemic therapies.

- Immunotherapy with monoclonal antibodies, either alone or in combination
  - A radioactive monoclonal antibody, such as **yttrium-90+ibritumomab tiuxetan** (Zevalin®), which is given by IV injection. Zevalin is a radioimmunotherapeutic agent that is approved for previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy and for relapsed or refractory CD20-positive, low-grade or follicular B-cell NHL.
  - **Obinutuzumab** (Gazyva®), an anti-CD20 monoclonal antibody given by IV infusion, is approved in combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen. It is also approved for the treatment of adult patients with previously untreated stage II bulky, III or IV FL in combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission.
  - The combination of the monoclonal antibody **rituximab** and the **endoglycosidase hyaluronidase human** (Rituxan Hycela™), given by subcutaneous injection, is approved by the FDA 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 cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

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

Transformed B-Cell Follicular Lymphoma (FL). Follicular lymphoma has a small risk of transforming into an aggressive large B-cell lymphoma, such as DLBCL. Patients with transformed B-cell FL appear to benefit from high-dose therapies along with autologous stem cell transplantation. (See *Diffuse Large B-Cell Lymphoma* on page 21.)

A clinical trial may be a good option for patients with disease that transforms after several different treatment approaches. Other options include

- Chemotherapy, either with or without **rituximab** (Rituxan®)
- Treatment with a radioimmunotherapeutic monoclonal antibody, such as **yttrium-90+ibritumomab tiuxetan** (Zevalin®)
- Radiation therapy
- Supportive care
- Autologous stem cell transplantation within a clinical trial. When an autologous stem cell transplant is an option, stem cells should be collected before treatment with radioimmunotherapy.

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):

- **No**des involved—5 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 g/dL.

Each point represents an increased risk for disease recurrence. The total number of points identifies the following risk groups: 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 treatment options, including participation in clinical trials.

Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome). Cutaneous T-cell lymphomas (CTCLs) are a group of non-Hodgkin lymphomas that develop primarily in the skin and may grow to involve lymph nodes, blood and other organs. This type of lymphoma originates in a T cell. Mycosis fungoides is the most common type of CTCL, and is characterized by prominent skin involvement. Mycosis fungoides 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 (SS)." 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 different forms of therapy 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); the combination therapy is often referred to as "PUVA" (psoralen and ultraviolet A) therapy.

Two agents that belong to the class of drugs called "histone deacetylase (HDAC)" inhibitors are used to treat CTCL. HDACs work by causing a chemical reaction in tumor cells, preventing them from dividing and leading to cell death. **Romidepsin** (Istodax®), given by IV infusion, is approved for patients who have received at least one prior systemic therapy. **Vorinostat** (Zolinza®), given by mouth, is approved for patients who have persistent or recurrent CTCL on or following two systemic therapies.

If there is widespread involvement of lymph nodes and other sites, either single- or multidrug chemotherapy or photopheresis can be used, depending on the objective of therapy and the rate of disease progression. Extracorporeal photopheresis (ECP) is an immunomodulatory therapy that uses PUVA. Leukocytes are removed by leukapheresis, then treated with psoralen, exposed to UVA and then returned to the patient. Extracorporeal photopheresis is recommended for patients either with, or at risk for, blood involvement, such as that seen in SS. Allogeneic stem cell transplantation may be considered for selected patients and this option can be potentially curative for some of them.

For more information about CTCL, see the free LLS booklet *Cutaneous T-Cell Lymphoma* Facts.

Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia (WM). Lymphoplasmacytic lymphoma 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 lymphoplasmacytic lymphoma, the lymph nodes are more involved than they are in WM. Both disorders show malignant lymphoplasmacytic cells in the marrow and spleen. Lymphoplasmacytic lymphoma is usually diagnosed by lymph node biopsy, while WM is diagnosed by marrow examination. These two types of lymphoma account for less than 2 percent of NHL cases.

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 is referred to as "hyperviscosity syndrome" which may require urgent intervention.

Hyperviscosity syndrome can be treated by plasmapheresis (a process in which plasma is separated from whole blood and the rest is returned to the patient). Plasmapheresis can reverse acute symptoms and signs, but long-term control requires a reduction in the mass of lymphoma cells that make the protein.

One option for patients without symptoms of WM is to take a watch-and-wait approach. Active treatment begins for these patients only if symptoms develop. Progressive disease may also involve the lungs, the gastrointestinal (GI) tract and other organs.

Most patients with WM are treated with combination chemotherapy. **R-CHOP** (rituximab [Rituxan®] plus cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], vincristine [Oncovin®] and prednisone) has been reported to produce excellent response rates.

The Bruton tyrosine kinase (BTK) inhibitor **ibrutinib** (Imbruvica®), given by mouth, is approved by the FDA for the treatment of patients with WM.

For more information about WM, see the free LLS fact sheet *Waldenström Macroglobulinemia* Facts.

Marginal Zone Lymphoma (MZL). This indolent B-cell lymphoma subtype may be extranodal (disease outside of the lymph nodes) or nodal (disease within the lymph nodes). It begins in B lymphocytes in a part of the lymph tissue called the "marginal zone." The disease tends to remain localized. **Ibrutinib** (Imbruvica®), a BTK inhibitor, is approved for patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy. There are several subtypes of MZL, each categorized by the type of tissue where the lymphoma forms.

- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma usually begins in the stomach. It forms in cells in the mucosa that help make antibodies. Patients with MALT lymphoma may have a history of autoimmune disease, such as Hashimoto thyroiditis or SS. A higher incidence of MALT lymphoma involving the stomach is seen in patients who have been infected with the bacterium *helicobacter pylori (H pylori)*. Bacteria have also been implicated in other forms of MALT lymphoma. Treatment often includes potent combinations of antibiotics, which both eliminate the infection and cause the lymphoma to regress. Many patients with *H pylori* infection have been cured of MALT lymphoma without radiation or chemotherapy. However, the presence of the translocation t(11;18) predicts a higher chance of not achieving remission and 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), and if this happens, patients can benefit from treatments used for DLBCL.
- Extragastric MALT lymphoma forms in cells of the mucosa that help make antibodies. It begins outside the stomach and can appear in almost every part of the body including other areas of the GI tract, salivary glands, thyroid, lung, skin and around the eye.

- Monocytoid B-cell lymphoma, also known as "nodal marginal zone lymphoma" (nodal MZL), may be found in the spleen and blood. This form of NHL is rare, accounting for less than 2 percent of NHL cases, and is generally treated like FL.
- Splenic marginal zone lymphoma (SMZL) is diagnosed in less than 1 percent of all NHL cases. SMZL 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 can be slow to develop. SMZL has been associated with hepatitis C infection. Treatment for hepatitis C with interferon (either alone or in combination with ribavirin) may result in a remission of the patient's 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** (rituximab [Rituxan®] plus cyclophosphamide [Cytoxan®],doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone)
    - **BR** (bendamustine hydrochloride (Bendeka), rituximab).

Researchers are investigating 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 small-cell lymphocytic lymphoma and are highly similar subtypes with regard to

- Incidence—median age of patients is 65 years
- Signs and symptoms—usually widespread enlarged lymph nodes (lymphadenopathy) and slight marrow and blood involvement
- Disease progression—may be very slow
- Treatment.

Chronic lymphocytic leukemia is primarily a disease of the blood and marrow; however, CLL cells may travel to the lymph nodes. SLL primarily involves lymph nodes or lymphoid tissue, and it represents about 7 percent of NHL cases.

The BTK inhibitor **ibrutinib** (Imbruvica®), given by mouth, is FDA approved for CLL/SLL and CLL/SLL with 17p deletion. The PI3K inhibitor **idelalisib** (Zydelig®), given by mouth, is approved for relapsed SLL patients who have received at least two prior systemic therapies. The BCL-2 inhibitor **venetoclax** (Venclexta®), given by mouth, is approved for use in patients who have CLL.

Bendamustine hydrochloride (Bendeka®), given by IV infusion, is a chemotherapy agent that is approved by the FDA for the treatment of patients with CLL and for patients with indolent B-cell NHL that has progressed either during or within 6 months of treatment with rituximab or a rituximab-containing regimen. 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 remission in patients with refractory disease. This therapy is under investigation in clinical trials.

For more information about CLL, see the free LLS booklet *Chronic Lymphocytic Leukemia*.

Refractory or Relapsed Non-Hodgkin Lymphoma (NHL)

In some patients, NHL does not respond to initial treatment. This is called "refractory" disease. In other patients, the lymphoma returns, even though these patients had achieved a remission. This is called "relapsed" disease.

Most patients with refractory or relapsed disease receive second-line therapy, in some cases followed by allogeneic (from a donor) or autologous (from the patient) stem cell transplantation. Second-line regimens may include

- **ICE**—Ifosfamide, carboplatin, and etoposide
- **RICE**—Rituximab, ifosfamide, carboplatin and etoposide
- **DHAP**—Dexamethasone, high-dose cytarabine (Ara-C®) and cisplatin (Platinol®)
- **ESHAP**—Etoposide, methylprednisolone, high-dose cytarabine (Ara-C®) and cisplatin (Platinol®)
- **R-ESHAP**—Rituximab, etoposide, methylprednisolone, high-dose cytarabine (Ara-C®) and cisplatin (Platinol®).

An elevated beta$_2$ microglobulin level, a high serum lactate dehydrogenase (LDH) level, expression of survivin (a protein that inhibits cell death), expression of cyclin D3, *p53* gene mutation and certain other factors are associated with higher risk for relapse after standard therapy. Imaging with a fluorodeoxyglucose positron emission tomography (FDG-PET) scan may be used to assess response after therapy to determine if there is a need for more aggressive therapy. Relapse is more common in the first 2 to 3 years after diagnosis but is rare 4 years after diagnosis.

Axicabtagene ciloleucel (Yescarta™), an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, is approved by the Food and Drug Administration (FDA) 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. Yescarta is not indicated for the treatment of patients who have primary central nervous system lymphoma.

Tisagenlecleucel (Kymriah™), a CD19-directed genetically modified autologous T-cell immunotherapy, is 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. Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

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

Relapsed Indolent Lymphoma. Slow-growing lymphoma often comes back after treatment, and new drug combinations may be required. A series of remissions lasting a number of years often occurs and patients can continue their usual activities for very long periods of time. Patients with low-grade lymphoma whose disease continues to progress after receiving other forms of treatment may benefit from autologous stem cell transplantation.

Bendamustine hydrochloride (Bendeka®), given by IV infusion, is approved by the FDA for patients with indolent B-cell NHL that has progressed either during or within 6 months of treatment with rituximab or with a rituximab-containing regimen. **Idelalisib** (Zydelig®), given by mouth, is FDA approved for use in patients who have relapsed small lymphocytic lymphoma or relapsed folllicular B-cell NHL who have received at least two prior systemic therapies.

Stem Cell Transplantation. Autologous stem cell transplantation after high-dose chemotherapy may be an option for some patients with lymphoma who have relapsed disease after R-CHOP chemotherapy. Autologous stem cell transplant is

a treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. Autologous stem cell transplantation allows patients with relapsed disease to receive intensive chemotherapy and rescue of their marrow function by infusion of stem cells. If an autologous transplant is not an option because of older age or medical complications, then treatment in clinical trials can be explored.

An allogeneic stem cell transplantation is a treatment that uses donor stem cells to restore a patient's marrow and blood cells. However, allogeneic transplant is not used as often as autologous stem cell transplantation because it is more toxic and is considered a last option.

New drugs and drug combinations are being tested in clinical trials for relapsed lymphomas.

Research and Clinical Trials

New approaches under study in clinical trials for NHL treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for NHL.

Clinical Trials. Every new drug or treatment regimen available has gone through a series of studies called "clinical trials" before it became a part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. When appropriate, personalized clinical-trial navigation by trained nurses is also available through our Clinical Trial Support Center (CTSC). Clinical Trial Specialists are registered nurses with expertise in blood cancers. They personally assist patients and caregivers throughout the entire clinical-trial process.

Research Approaches. There are clinical trials for newly diagnosed patients and for patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with non-Hodgkin lymphoma (NHL).

Agents Under Study. The following drugs are examples of specific agents under study:

- **Brentuximab vedotin** (Adcetris®) targets cluster designation (CD) 30 (CD30) and is used for treating peripheral T-cell lymphomas and Hodgkin lymphomas. It is under study in clinical trials for treating other previously treated NHLs.
- **Yttrium-90+ibritumomab tiuxetan** (Zevalin®) is approved by the Food and Drug Administration (FDA) for previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy and for relapsed/refractory follicular patients. The effectiveness of this agent is now being studied in the retreatment of lymphoma, as therapy for newly diagnosed indolent lymphoma, as therapy for aggressive forms of NHL in combination, either with or following other drug regimens, and as part of high-dose therapy programs along with autologous stem cell transplantation.
- **Ofatumumab** (Arzerra®) is an anti-CD20 antibody that is approved by the FDA for treatment of relapsed chronic lymphocytic leukemia (CLL). It is now being studied in clinical trials in various combinations for the treatment of mantle cell, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma.
- **Obinutuzumab** (Gazyva®) is an antibody that targets CD20. It is being used in the treatment of some types of NHLs including refractory follicular lymphoma. It is being studied in clinical trials (in combination with other agents) for treating relapsed and refractory CLL and small-cell lymphocytic leukemia (SLL).
- **Blinatumomab** (Blincyto®), a bispecific antibody that targets CD19 and CD3, is under investigation for heavily pretreated patients DLBCL and indolent lymphoma.
- **Mogalizumab** (Poteligeo) is a monoclonal antibody that targets chemokine receptor 4 (CCR4). It is in clinical trials for the treatment of patients with cutaneous T-cell lymphoma and adult T-cell leukemia/lymphoma.
- **Idelalisib** (Zydelig®), is a PI3K inhibitor which is approved by the FDA for the treatment of chronic lymphocytic leukemia and for the treatment of refractory indolent NHL. This agent is being explored in combination with chemotherapy, monoclonal antibodies and other new drugs for the treatment of heavily pretreated for relapsed or refractory indolent B-cell NHL, mantle cell lymphoma (MCL) and marginal zone lymphoma patients.
- The **oral selective inhibitor of nuclear export (SINE) selinexor (KPT-330)** is being studied for the treatment of DLBCL. This drug acts by blocking the transport of nuclear proteins in malignant cells, leading to cell death.
- **Antifolate pralatrexate** (Foloytn®), approved for various T-cell lymphoma subtypes, is being studied as a single agent and in combination with other chemotherapy drugs for treating various relapsed and refractory B-cell and T-cell NHLs. Pralatrexate is an antifolate drug that disrupts processes in cells that are required for cell replication.

- **mTOR inhibitors** work to slow or inhibit the progression of MCL by reducing cell expression of cyclin D1 and other important proteins responsible for cancer cell growth. Blocking mTOR activity in MCL leads to antiproliferative effects and, sometimes, to cell death. They have demonstrated activity in MCL alone and in combination with other therapies. Examples of mTOR inhibitors is under investigation include
  - **Temsirolimus** (Torisel®) for treatment of relapsed MCL. Several studies are evaluating temsirolimus as combination therapy with conventional chemotherapy (single agent or combination), immunomodulatory agents (eg, lenalidomide), monoclonal antibodies (eg, rituximab), alkylating agents (eg, bendamustine) and proteasome inhibitors (eg, bortezomib) for untreated and for relapsed/refractory MCL.
  - **Everolimus** (Afinitor®) is a medication that blocks cancer proliferation by cutting off the blood supply to cancer cells. This agent is being studied in patients with advanced, refractory, or relapsed MCL. This drug is also being studied in combination with other drugs, such as lenalidomide, bortezomib and bendamustine/rituximab, for relapsed MCL.
- **Cell cycle inhibitors** interfere with the process of cell division that enables tumors to grow.
  - **Palbociclib** (Ibrance®) is a cyclin D-dependent kinase 4/6 (CDK4/6) inhibitor that decreases tumor cell proliferation and sensitizes ibrutinib-resistant MCL cells to PI3K inhibitors. It is being studied in clinical trials as a single agent and in combination with other drugs such as bortezomib and ibrutinib for relapsed and refractory MCL patients. It is also being studied in combination with other drugs to treat various indolent and aggressive NHLs.
  - **Abemaciclib** (Verzenio®), a CDK 4/6 inhibitor, has also shown clinical activity in heavily pretreated MCL and is being studied in clinical trials.
  - **Flavopiridol** (Alvocidib®) is a pan-CDK inhibitor being studied in combination with fludarabine and rituximab for both newly diagnosed and previously treated MCL. Another study, currently in trials, combines flavopiridol and bortezomib for the treatment of relapsed MCL and the combination is being found to be safe and well tolerated.
- **Lenalidomide** (Revlimid®) is an immunomodulator, which regulates the function of the immune system and has the capability of slowing the rate at which cancer cells grow and multiply, is FDA approved for the treatment of patients who have relapsed or refractory MCL. This drug may be given if first-time treatment does not work. It is being studied as monotherapy and in combination with rituximab and/or other agents in patients who have relapsed or refractory DLBCL, MCL, follicular lymphoma and CLL.

- **Proteasome inhibitors** affect cell pathways by blocking the activity of enzymes that are needed for cell proliferation and survival.
  - **Bortezomib** (Velcade®), which may also stop the growth of cancer cells by blocking blood flow to the tumor, is being studied together with rituximab and some chemotherapy combinations in both untreated and refractory MCL and for other aggressive NHLs.
  - **Carfilzomib** (Kyprolis®), which is FDA approved for the treatment of patients with multiple myeloma, is in clinical studies as single-agent therapy and as combination therapy for patients with relapsed/refractory MCL. Carfilzomib works by preventing cancer cells from repairing themselves, which may cause cell death.
- **Vorinostat** (Zolinza®) is a histone deacetylase (HDAC) inhibitor which are a class of drugs that address "epigenetic" changes in the DNA and cause a chemical reaction in tumor cells, preventing them from dividing. It has shown promising results in newly diagnosed MCL, especially when it is used in combination with other agents, such as rituximab and cladribine.
- **Reduced-Intensity Stem Cell Transplantation (Nonmyeloablative Allogeneic Transplantation)** may be a an option for older and sicker patients. Clinical trials are under way to evaluate this type of transplantation and determine its effectiveness as treatment for many blood cancers, including some NHL subtypes. As a result, stem cell transplantation may be a possible treatment for patients aged 60 to 70 years and older. Patients undergo conditioning for a reduced-intensity transplant; they receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft (the donor immune cells), thereby allowing the engrafted immune cells to attack the recipient's disease. 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.
- **Chimeric antigen receptor (CAR) T-cell therapy** is a type of immunotherapy that consists of engineering a patient's own immune cells to recognize and then attack cancerous tumors. This approach has shown very promising results in patients with blood cancers. The patient's T cells are genetically engineered to produce CARs on their surface. These receptors recognize and bind to a specific target found on the cancer cells. Axicabtagene ciloleucel (Yescarta™) and tisagenlecleucel (Kymriah™) are currently approved for lymphoma.

  For more information on this type of therapy, please see the LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy* Facts.

Nivolumab (Opdivo®) is a programmed cell death 1 (PD-1) checkpoint inhibitor that has shown positive results in other cancers, such as melanoma. Nivolumab is being studied both as a single agent and in combination with other drugs for the treatment of B-cell and T-cell NHLs.

Pidilizumab is a PD-1 checkpoint inhibitor. It is being studied in clinical trials for the treatment of relapsed follicular lymphoma.

We encourage you to contact an Information Specialist for more information about specific treatments under study in clinical trials.

Side Effects of Treatment

The side effects of treatment for lymphoma depend on the intensity and type of treatment, such as the location of the radiation therapy, the age of the patient, and 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 trouble many patients, such as nausea and vomiting. When side effects do occur, most are short-lived and resolve when therapy is completed. The benefits of treatment, with the goal of remission (and in some cases, cure) generally outweigh the risks and discomfort associated with NHL therapy. For more information, see the free LLS booklet *Understanding Side Effects of Drug Therapy.*

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, 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 counts to recover from the effects of treatment. To stimulate the production of depleted numbers of white blood cells, a granulocyte-colony stimulating factor (G-CSF) such as Neupogen® or Neulasta® is sometimes used. This subcutaneous injection is given 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 non-Hodgkin lymphoma (NHL) such as splenic marginal zone lymphom, also contributes to the risk of severe infection.

Improvement in the treatment of patients with NHL, increased awareness of the risk of infectious diseases and better antimicrobial therapy have made infectious complications less of a medical problem for patients.

NHL patients are advised to receive certain vaccinations once they have finished their treatment, including vaccinations for pneumococcal pneumonia and influenza. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations that should not be administered include those using live organisms or those with high viral loads, such as the herpes zoster (shingles) vaccine. Your doctor can give you more information.

Viral Reactivation. Hepatitis B virus (HBV, 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 anti-cluster designation (CD) 20 (CD20) monoclonal antibodies (rituximab [Rituxan], ofatumumab [Arzerra], 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 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.

Neuropathy. Some chemotherapeutic agents, such as the drug 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 come and go, 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 dose of vincristine may need to be adjusted.

Progressive Multifocal Leukoencephalopathy (PML). This is a 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 AIDS patients or blood cancer patients, who have profound immunosuppression due to the underlying disease or its treatment. The use of rituximab (used 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.

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). TLS is characterized by metabolic abnormalities that are caused by the sudden release of the cellular contents of dying cells into the bloodstream, a phenomenon induced by chemotherapy. 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.

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

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

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 longer periods that can affect learning. For more information, 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 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 and for 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, including inflammation of the sac surrounding the heart (the pericardium), valve dysfunction or 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. Therapy with autologous bone marrow or peripheral blood stem cell transplant and treatment with chemotherapy-containing alkylating agents are associated with an increased risk of developing myelodysplastic syndrome and acute myeloid leukemia.

Fertility. Patients may be less fertile after treatment for NHL. The risk of infertility varies according to the nature of the treatment, including the type and amount of chemotherapy, the location of radiation therapy and the patient's age. Men who are at risk of infertility should consider sperm banking before treatment and women should discuss all of their fertility 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. In 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, see the free LLS booklets *Fertility* Facts*; Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma* Facts*;* and *Long-Term and Late Effects of Treatment in Adults* Facts.

Follow-up Care. Follow-up care is important with both aggressive and indolent forms of NHL because if the disease recurs, curative options are still available for many people. Follow-up care needs to be individualized and should be based on several factors, including how the disease initially manifested. Patients who are in remission should continue to be monitored by clinical assessment as determined by their doctor. In the past, computed tomography (CT) scans or other diagnostic imaging were done routinely in an attempt to detect relapse. However, there is an increasing awareness that too many scans may be harmful, and that CT scans performed in otherwise asymptomatic patients have a relatively low chance of finding recurrent lymphoma. The frequency of clinical visits, laboratory tests, and CT scans or other imaging 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 74,680 new cases of non-Hodgkin lymphoma (NHL) are expected to be diagnosed in the United States in 2018. Most of these cases (about 85 to 90 percent) comprise one of 14 different types of NHL that involve lymphocytes called "B cells." The two most common subtypes of NHL, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, are examples of B-cell lymphomas. The other approximately 10 to 15 percent of cases of NHL involve lymphocytes called "T cells" or "natural killer (NK) cells." T-cell lymphoma includes peripheral T-cell lymphoma and cutaneous T-cell lymphoma.

NHL 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. NHL is most frequently diagnosed among people 80 to 84 years old (see Figure 4).

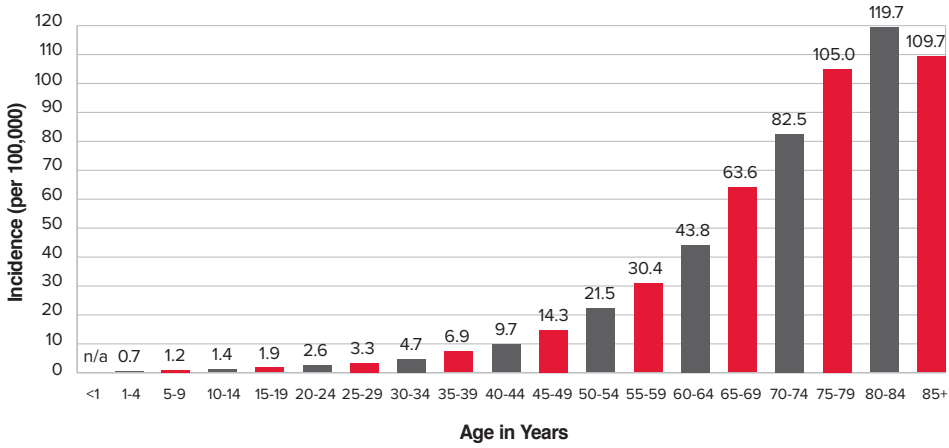

Figure 4. The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of non-Hodgkin lymphoma each year per 100,000 people, by age-group. The incidence of non-Hodgkin lymphoma significantly increases with age. Fewer than 7 cases per 100,000 occur in people in their late 30s. Incidence increases progressively to 119.7 cases per 100,000 in persons age 80 to 84. Source: The Leukemia & Lymphoma Society. Facts 2017-2018.

Causes and Risk Factors. The exact cause of NHL is not known but there are risk factors that may increase a person's likelihood of developing the disease. Factors affecting an individual'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).
- Genome-wide (entire set of genetic instructions found in a cell)-association studies have found loci (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 human immunodeficiency virus infection and acquired immune deficiency syndrome (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 farming has been linked to NHL overall and to major NHL subtypes. 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 ingredients in herbicides and pesticides, such as organochlorine, organophosphate and phenoxy acid compounds, are linked to lymphoma. For example, the occupational exposure to nonarsenical insecticides during spraying and application has been classified by the International Agency for Research on Cancer as a "probable human carcinogen" for NHL. The number of lymphoma cases caused by such exposures 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 infection with either a virus or a 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 is strongly associated with Burkitt lymphoma in Africa. 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 persons whose immune systems are suppressed as a result of organ transplantation and its associated therapy. Epstein-Barr virus infection is closely associated with both Burkitt lymphoma and nasal 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.
  - Human immunodeficiency virus infection and acquired immune deficiency syndrome (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* and *Chlamydia psittaci* are thought to be associated with the development of marginal zone lymphomas.
  - The bacterium *Coxiella 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 under "Blood Cancer—General Information" and then click on "Disease registries and other disease studies."

Normal Blood and Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients to living cells and carries away the cells' waste products. It also contains immune cells to fight infections and platelets that can stop bleeding in damaged blood vessels.

Blood is composed of plasma and cells.

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

- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors) that are made by the liver.
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production.
  - Immunoglobulins, proteins that help the body fight infection.
- Hormones, such as insulin and corticosteroids
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B_{12}
- Electrolytes, such as calcium, potassium and sodium.

Blood cells. There are three types of blood cells suspended in the plasma. They are

- 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, which is a protein that picks up oxygen from the lungs and delivers it to the cells throughout the body. Hemoglobin then picks up carbon dioxide from the cells and delivers it to the lungs where it is removed when a person exhales.

- Platelets
  - Are fragments of cells (one-tenth the size of red blood cells)
  - Help stop bleeding from an injury. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the blood vessel, clump together and plug up the bleeding site with the help of blood-clotting proteins, such as fibrin and electrolytes such as calcium.
- White blood cells (cells that fight infections). There are several types of white blood cells, including
  - Neutrophils. A type of immune cell that is a "phagocyte" (eating cell). It helps fight infection by ingesting microorganisms and releasing enzymes that kill the microorganisms. It is a type of granulocyte, a white blood cell that has small particles.
  - Eosinophils. A type of immune cell that has granules (small particles). It plays an important role in the body's response to allergic reactions and infection with parasites.
  - Basophils. A type of immune cell that has granules (small particles). It plays a role during allergic reactions and asthma.
  - Monocytes. A type of immune cell that is a phagocyte. It can leave the bloodstream and enter tissues to attack invading organisms and fight off infection. It surrounds and kills microorganisms, ingests foreign material and removes dead cells.
  - Lymphocytes. This type of white blood cell is found mostly in the lymph nodes, spleen and lymphatic channels. It is a key part of the immune system. There are three major types of lymphocytes. They are
    - T lymphocytes (T cells)
    - B lymphocytes (B cells)
    - Natural killer (NK) cells.

New red blood cells, platelets and most white blood cells are formed in the bone marrow, a spongy tissue that is found in the central cavity of bones. The creation of new blood cells is controlled by the body's needs. The human body generates billions of new blood cells every day to replace old and worn out cells. Certain events also may prompt the body to produce additional blood cells. For example, the bone marrow will produce and release more white blood cells in response to an infection.

While red blood cells, white blood cells and platelets vary in appearance and function, they all originate from a single type of unspecialized cell called a "hematopoietic stem cell." Hematopoietic (blood-forming) stem cells are found in the bone marrow of the femurs (thigh bones), hips, vertebrae (back bones) and the ribs. An unspecialized hematopoietic stem cell can give rise to specialized cells that have specific functions. For example, a hematopoietic stem cell can give rise to a red blood cell that carries oxygen throughout the body, or it can give rise to a neutrophil, a white blood cell, that helps fight infections. The process by which an immature cell becomes a mature cell with specific functions is called "differentiation."

The process of creating new blood cells through differentiation is called "hematopoiesis" (see Figure 5 on page 52). When a stem cell divides, each "daughter" cell has the potential to either remain a stem cell or to become a specialized cell, such as a red blood cell, a white blood cell or a platelet. For those cells "committed" to specialize, the stem cell generates an intermediate cell. The intermediate cell is called a "precursor" or "progenitor" cell. While the stem cell remains in an immature, unspecialized state, the progenitor cell divides and undergoes multiple stages of development, becoming more specialized at each stage, until it becomes a particular type of mature blood cell.

The hematopoietic stem cell can give rise to lymphoid stem cells and myeloid stem cells. The lymphoid stem cells create lymphoid progenitor cells. Different types of progenitor or precursor cells develop into different types of mature blood cells. Through the process of differentiation, lymphoid progenitor or precursor cells mature into T cells, B cells or NK cells.

Myeloid stem cells create myeloid progenitor cells. These precursor or progenitor cells will develop into mature blood cells including red blood cells, platelets and certain types of white blood cells (eosinophils, basophils, neutrophils and monocytes.) For example, a myeloid progenitor cell will go through various stages of development to become a neutrophil: myeloid progenitor → promyelocyte → myelocyte → metamyelocyte → band → neutrophil. In healthy people, stem cells in the bone marrow produce new blood cells continuously. Once the blood cells have matured, they leave the bone marrow and enter the bloodstream.

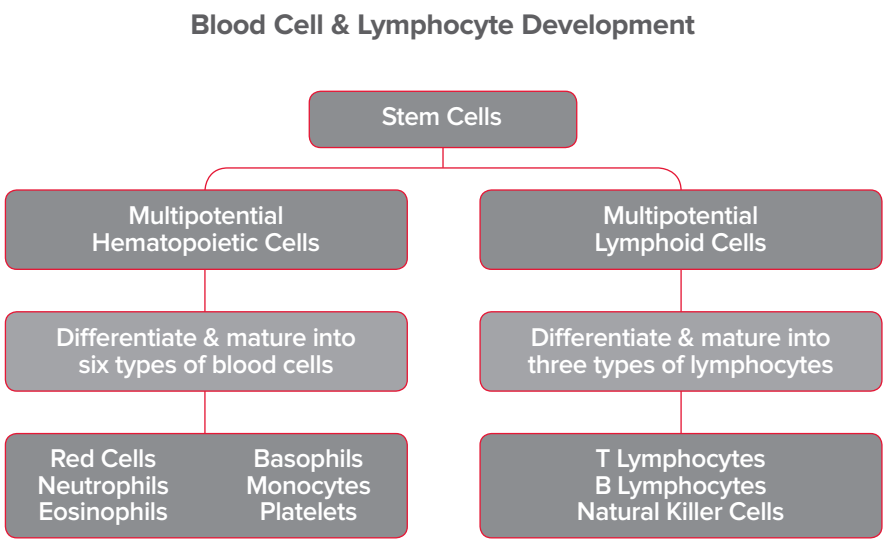

Figure 5. Stem cells develop into blood cells (hematopoiesis) and lymphoid cells.

The Lymphatic System

The marrow is really two organs in one. The first is marrow as the blood cell-forming organ. The second is marrow as the lymphocyte-forming organ that is a part of the immune system.

The marrow produces three main types of lymphocytes (white blood cells). They are

- B lymphocytes (B cells), which make antibodies in response to foreign substances (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 another white blood cell to recognize the antibody and "ingest it," that is, pull it into the cell along with its attached microbe. The white cell then kills and digests the microbe.
- Natural killer (NK) cells, which attack virus-infected cells without requiring 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 (special lymph nodes), 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 of the booklet lists various resources that can be helpful to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team members' knowledge and skills.

For Help and Information

Consult with an LLS 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, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists.

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

Some of the free LLS booklets include

- *Blood and Marrow Stem Cell Transplantation*
- *Blood Transfusion*
- *Chimeric Antigen Receptor (CAR) T-Cell Therapy*
- *Cutaneous T-Cell Lymphoma* Facts
- *Fertility* Facts
- *Immunotherapy* Facts
- *Long-Term and Late Effects of Treatment in Adults* Facts
- *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma* Facts
- *Mantle Cell Lymphoma* Facts
- *Peripheral T-Cell Lymphoma* Facts
- *Understanding Clinical Trials for Blood Cancers*
- *Understanding Side Effects of Drug Therapy*
- *Waldenström Macroglobulinemia* Facts

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

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.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations by a registered dietitian with experience in oncology nutrition. Assistance with healthy eating strategies, side effect management, and survivorship nutrition as well as provide additional nutrition resources. For more information, please visit www.LLS.org/nutrition.

Podcast. Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients. The Bloodline with LLS is here to remind you that after a diagnosis comes hope. For more information and to subscribe, visit www.LLS.org/TheBloodline.

Suggested Reading. A list of select books that are recommended for patients, caregivers, children and teens. To find out more, visit www.LLS.org/SuggestedReading.

Continuing Education. LLS offers free continuing education programs for healthcare professionals. For more information, please visit www.LLS.org/ProfessionalEd.

Community Resources and Networking

LLS Community. This is a one-stop virtual meeting place for chatting with other patients and staying up-to-date on the latest diagnosis and treatment news. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. To join, visit www.LLS.org/community.

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

- **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.

Clinical Trials (Research Studies). New treatments for patients are under way. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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). For more information, please visit www.LLS.org/espanol.

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

Children. NHL is rare in children. Families face new and unfamiliar treatments and care protocols. The child, parents and siblings may all need support. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/booklets to read or order the free LLS booklet *Coping with Childhood Leukemia and Lymphoma.*

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.

Feedback. To give suggestions about this booklet, visit www.LLS.org/PublicationFeedback.

Health Terms

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. Allogeneic transplantation, an investigational therapy, may be considered in the treatment of indolent NHL, particularly for younger patients whose disease behaves more aggressively than the average indolent lymphoma. A type of allogeneic transplant called a "reduced-intensity" or "nonmyeloablative" transplant is under study. It uses lower doses of conditioning therapy and may be safer, especially for older patients. For more information, 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.

Antioncogene. See Tumor Suppressor Gene.

Apheresis. The process of removing certain components of a donor's blood and returning the unneeded parts to the donor. The process, also called "hemapheresis," uses continuous circulation of blood from a donor through a specialized machine and then back to the donor. 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 diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma, an autologous transplant in first remission may be a good treatment option. For more information, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

***BCL-2* Gene Rearrangement.** Rearrangement in the *BCL-2* gene that occurs in B cells and is present in many cases of follicular lymphoma, diffuse large B-cell lymphoma and other cancers.

Biopsy. A procedure to obtain tissue for diagnosis. 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 nodes may be necessary (lymph node biopsy).

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In these sites, the marrow is filled with fat cells. 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 test to examine marrow cells to detect cell abnormalities. A marrow sample is usually taken from the patient's hip bone. After a local anesthetic is given to numb the skin, the liquid sample is aspirated (removed) using a special needle that is inserted through the bone into the bone marrow.

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. Bone marrow aspiration and bone marrow biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together.

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

Central Line (Indwelling Catheter). A special tubing inserted into a large vein in the upper chest. The central line, sometimes referred to as an "indwelling catheter," is tunneled under the skin of the chest to keep it firmly in place. The external end of the catheter can be used to administer medications, fluids or blood products or to withdraw blood samples. See Port.

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

Chromosome. 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 and thus are monoclonal. Leukemia, lymphoma and myeloma are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Cluster Designation (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®]).

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 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. The genetic material in the cell. "Deoxyribonucleic acid" is the scientific name for DNA, which is made up of a sugar-phosphate backbone with ladderlike "steps" composed of purines and pyrimidines (building blocks of nucleic acids). The sequence of the purines and pyrimidines in the DNA 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.

DNA-Gene Chip. See Microarray.

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

Epigenetic Change. Any change that alters gene activity without changing the DNA sequence. While epigenetic changes are natural and essential to many of the body's functions, certain epigenetic changes can cause major adverse health effects, including cancer.

Erythrocytes. See Red Blood Cells.

Erythrocyte Sedimentation Rate. See Sedimentation Rate.

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."

FISH. See Fluorescence In Situ Hybridization.

Flow Cytometry. A test that permits the identification of specific cell types within a sample of cells. The test may be used to examine blood cells, marrow cells or cells from a biopsy. One use of flow cytometry is to determine whether a sample of cells is composed of T cells or B cells. This permits 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 using DNA probes tagged with fluorescent molecules that emit light of different wavelengths (and in different colors). The probes match 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 turned off or on 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. GM-CSF can also stimulate monocytes.

Hemapheresis. See Apheresis.

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. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells such as red blood cells or white blood cells of various types. This process is called "differentiation." The young or 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. Hematopoiesis is a continuous process that is active normally 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.

HLA. The abbreviation for "human leukocyte antigen(s)." These antigens are proteins on the surface of most tissue cells, and they give an individual his or her unique tissue type. HLA factors are inherited from mother and father, and the greatest chance of having the same HLA type is between siblings. On average, one in four siblings is expected to share the same HLA type. The testing for HLA antigens is referred to as "tissue typing."

Immunophenotyping. A method that uses the reaction of antibodies with cell antigens to determine a specific type of cell in a sample of blood cells, marrow cells 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. The tag can be identified 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* Facts.

Indwelling Catheter. See Central Line.

Intrathecal. Designation for the space between the covering or lining of the central nervous system (CNS) and the brain or spinal cord. That lining 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 are 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 is often elevated in lymphoma and lymphocytic leukemias. Changes in LDH are nonspecific, but when LDH is elevated in the presence of lymphocytic cancers, the change may reflect the extent of the tumor and the rapidity of tumor growth. LDH monitoring is used in some cases along with other measures to plan the intensity of therapy for lymphoma. Burkitt lymphoma and other types of aggressive lymphoma are often associated with marked elevations in the levels of serum LDH. Also known as "lactic acid dehydrogenase."

Leukocytes. See White Blood Cells.

Leukopenia. A decrease below normal values in the concentration of blood leukocytes (white blood cells).

Lymphadenopathy. Enlargement of lymph nodes.

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, and 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 grow and the lymph nodes may become enlarged. This enlargement of lymph nodes can be seen, felt 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 the essential cell type in 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 testing technique that provides detailed images of body structures. It differs from the 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 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.

Maturation. See Hematopoiesis.

Meninges. See Intrathecal.

Microarray. A two-dimensional grid of molecules (often, but not always, DNA genes or gene fragment spots), usually arranged on a glass slide or silicone wafer. A typical microarray (also called a "DNA-gene chip") contains 10,000 to 200,000 microscopic DNA spots. Scientists use a microarray to study gene expression and to learn which genes are either expressed or not expressed under given circumstances. See Gene Expression Profiling.

Monoclonal. See Clonal.

Monoclonal Antibody Therapy. See Immunotherapy.

Monocyte/Macrophage. A type of white blood cell that represents 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 the tissue, they are converted to 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 that represents the gene. A "germ cell mutation" is present in the egg or the sperm and can be transmitted from parent to offspring. A "somatic mutation" 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. In leukemia, lymphoma or myeloma, a primitive marrow (blood-forming) or lymph node cell undergoes a somatic mutation or mutations that lead to the formation of a tumor. If a mutation results from a major abnormality of chromosomes such as a translocation, it can be detected by cytogenetic examination. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the oncogene.

Neutropenia. A decrease below normal values in the 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 patients 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.

Oncogene. A mutated gene that is the cause of a cancer. Several subtypes of acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma, and nearly all cases of chronic myeloid leukemia are associated with an oncogene.

Oncologist. A doctor who diagnoses and treats patients with cancer. Oncologists are usually internists who undergo additional specialized training to treat adults with cancer (or pediatricians, who treat children). 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 (surgery, radiation therapy, chemotherapy or immunotherapy) for the patient.

Pathologist. A doctor who identifies disease by studying tissues under a microscope. A hematopathologist is a type of pathologist who studies diseases of blood cells by looking at peripheral blood smears, bone marrow aspirates and biopsies, lymph nodes and other tissues and uses his or her expertise to identify diseases such as NHL. In addition to the microscope, a hematopathologist also uses laboratory values, flow cytometry and molecular diagnostic tests to make the most accurate diagnosis. The hematopathologist works closely with the hematologist or oncologist who sees the patient and decides on the best treatment based upon the diagnosis.

Percutaneously Inserted Central Venous Catheter (PICC or PIC Line). A long, thin, flexible tube that is inserted into the body and can be left in place for weeks or even months for administration of medications, fluids and nutrition. It can also be used to obtain blood samples. The PICC eliminates the need for standard intravenous (IV) administration.

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. They leave the blood and enter tissues in which an infection has developed. Chemotherapy and radiation can cause a severe decrease in the concentrations of these cells which makes patients more susceptible to infection. Treatment may suppress blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

PICC or PIC line. See Percutaneously Inserted Central Venous Catheter.

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).

Polymerase Chain Reaction (PCR). A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied or determined. This technique has become useful in detecting a very low concentration of residual lymphoma cells, too few to be seen using a microscope. PCR can detect the presence of one lymphoma cell among 500,000 to 1 million nonlymphoma cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the lymphoma cells in order to be used for identifying residual abnormal cells.

Port. A small device, attached to the end of a central line (catheter),that provides access to the vein. The port is placed under the skin of the chest. After the site heals, no dressings or any special home care is required. To give medicines or nutrition or to take blood samples, the doctor or nurse inserts a needle through the skin into the port. A numbing cream can be put on the skin before the port is used.

Positron Emission Tomography (PET) Scan. A procedure used to image lymphoma masses. In this technique, glucose, a type of sugar, is labeled with a positron particle emitting a radioisotope such as fluorine-18. The utilization of sugar is greater in lymphoma cells than in normal tissue, and the isotope thus becomes concentrated in areas of lymphoma. The location of the lymphoma sites in the body can be identified by scanning for intense positron particle emission. PET is combined with computed tomography (CT) to establish the precise location of lymphoma masses; compared to other imaging procedures, PET can detect much smaller lymphoma masses. In some cases, successfully treated lymphoma may convert to fibrous tissue that 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 (primarily fibrous) do not take up the fluorine-18-labeled sugar, PET can distinguish residual lymphoma from healed scar tissue. PET is increasingly used for both staging of lymphoma and assessing response.

Radiation Therapy. The use of x-rays and other forms of radiation in treatment. Radiation therapy may be useful in the treatment of localized lymphoma. 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 adjunct to therapy when there are particularly large masses of lymphoma in a localized area or when local large 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 (erythrocytes) 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.

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. A 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. Long-term benefit usually requires a complete remission, especially in progressive lymphomas.

RNA. Abbreviation for ribonucleic acid, a molecule in cells that carries out DNA's instructions for making proteins.

Sedimentation Rate. A blood test that measures how quickly red blood cells (erythrocytes) settle in a test tube in 1 hour. A sedimentation rate test is done to find out if inflammation is present in the body, to check on the progress of a disease or to see how well a treatment is working. This test is also called a "sed rate" or "erythrocyte sedimentation rate (ESR)."

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. Primitive cells in marrow that are essential to the formation of red blood cells, white blood cells and platelets. Stem cells are largely 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.

Thrombocyte. See Platelets.

Thrombocythemia. An increase above the normal concentration of platelets in the blood.

Thrombocytopenia. A decrease below the normal 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 training and development of T lymphocytes (T cells). The human thymus becomes much smaller at the approach of puberty.

Toxin. A naturally derived substance that is poisonous to cells. A toxin can be attached 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.

Tumor Suppressor Gene. A gene that acts to prevent cell growth. If a mutation occurs that "turns off" this gene and causes loss of function, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurred. Another term for tumor suppressor gene is "antioncogene."

White Blood Cells. Any of the five major types of infection-fighting white cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. White cells are also called "leukocytes."

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