

## Non-Hodgkin Lymphoma (Lymphoid Neoplasms)

### Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. These cancerous lymphocytes can travel to different parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

Overall, NHL is the fifth most common cancer affecting adults in the United States. The incidence of NHL in the United States nearly doubled between 1975 and 2013, while the rates have plateaued over the last several years. In 2016, more than 72,000 new cases were expected to be diagnosed.

NHL is not a single disease, but rather a group of several closely related cancers, called lymphoid neoplasms. The most recent 2016 revision of the World Health Organization classification of lymphoid neoplasms estimates that there are approximately 85 subtypes of NHL. Among these, three lymphoma subtypes make up the majority of NHLs. These most common types of NHL in the United States are diffuse large B-cell lymphoma (22%), chronic lymphocytic leukemia/small lymphocytic lymphoma (18%), and follicular lymphoma (11%). Although the various types of NHL share many common characteristics, they differ in certain features, including their appearance under the microscope, their molecular features and growth patterns, their impact on the body, and how they respond to different types of treatment. For more in-depth information on NHL, please see the Lymphoma Research Foundation's (LRF's) booklet *Understanding Non-Hodgkin Lymphoma: A Guide for Patients, Survivors, and Loved Ones* at [www.lymphoma.org/publications](http://www.lymphoma.org/publications) or call the LRF Lymphoma Helpline at 800-500-9976 to order a copy.

NHL is broadly categorized into two groups: B-cell lymphomas and natural killer (NK)/T-cell lymphomas. B-cell lymphomas develop from abnormal B cells and account for about 85 to 90 percent of all NHLs. NK/T-cell lymphomas develop from abnormal T cells or NK cells and account for about 10 to 15 percent of all NHLs. NHL subtypes are also classified as either *indolent* (slow-growing) or *aggressive* (fast-growing).

Common signs and symptoms of NHL include swelling of the lymph nodes (which is often but not always painless), fever, night sweats, unexplained weight loss, and lack of energy. While most people with these symptoms will not have NHL, anyone with *persistent symptoms* (lasting more than several weeks) should be seen by a physician.

### Diagnosis and Staging

A biopsy of an affected lymph node or a sample of the tumor is the only way to make a definite diagnosis of NHL. The most acceptable type of surgical biopsy is called an "excisional biopsy." A *pathologist* (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples) or a *hematopathologist* (pathologist who has undergone additional training in the diagnosis of blood diseases, including lymphoma) who is experienced in diagnosing lymphoma should review the biopsy. There are multiple subtypes of NHL, many of which are very uncommon, and highly specialized procedures and tests may be needed in order to make an accurate diagnosis. An accurate diagnosis and exact NHL subtype help identify appropriate treatment options to most effectively treat the patient's particular subtype of lymphoma.

Generally speaking, NHL is a *systemic* (throughout the body) disease. Staging is used to describe where the cancer is located and how widely the cancer has spread in patients with NHL. The Lugano Classification of the Ann Arbor staging system is used for most NHLs. To stage a patient's disease, the physician may order imaging tests such as abdominal and chest computed tomography (CT) scans or a positron emission tomography (PET) scan. Other tests may include a bone marrow biopsy, spinal tap, echocardiogram, magnetic resonance imaging scan, and additional blood tests.

## Risk Factors

The characteristics that make a person possibly more susceptible to developing any type of disease are called risk factors. Having one or more risk factors does not mean a person will develop NHL. In fact, most people with the known risk factors never develop NHL, and many people diagnosed with NHL do not have any of these risk factors. The causes of NHL in most cases remain unknown. Nevertheless, known risk factors for NHL include:

- A weakened immune system caused by an inherited immune disorder (for example, hypogammaglobulinemia or Wiskott-Aldrich syndrome) or infection with human immunodeficiency virus (HIV; the virus that causes AIDS)
- An autoimmune disease (for example, Crohn disease, rheumatoid arthritis, systemic lupus erythematosus, or psoriasis)
- Treatment for autoimmune diseases, especially with methotrexate and tumor necrosis factor (TNF)-inhibitor therapy
- Treatment with certain drugs used after organ transplantation
- Infections with certain viruses (for example, Epstein-Barr virus [EBV], human T-cell lymphotropic virus type 1 (HTLV-1), or hepatitis C virus [HCV])
- Infection with the bacteria *H. pylori*, *Campylobacter jejuni*, or *Chlamydia psittaci*
- Older age — Like most cancers, NHL is much more common in adults older than 60, although it may develop in children and adults of all ages
- Male sex (for unknown reasons, NHL is slightly more common in men than in women)
- Exposure to certain chemicals such as some herbicides (for example, Agent Orange) and pesticides, and some chemotherapy drugs used to treat other cancers or autoimmune diseases
- Treatment with radiation therapy for other cancers, including NHL

## Types and Subtypes of NHL

The classification of lymphoma is complicated and has evolved over the years. NHL subtypes are grouped according to which kind of lymphocyte is affected (B cells or NK/T cells) and how quickly the cancer grows (aggressive or indolent). Within each type of lymphoma (for example, B cell), there are many subtypes. There are more subtypes of NHL than those listed here. Please consult with a physician if you are not sure of your subtype. New next-generation molecular sequencing studies and cytogenetic studies are defining different subsets that are clinically meaningful. The following list includes selected lymphoid malignancies in the current World Health Organization (WHO) classification.

### *Aggressive B-Cell NHLs include the following subtypes:*

- Burkitt/Burkitt-like lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Double-hit lymphoma
- Mantle cell lymphoma (MCL)
- Primary mediastinal B-cell lymphoma

### *Aggressive T-Cell NHLs include the following subtypes:*

- Anaplastic large cell lymphoma (ALCL)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Peripheral T-cell lymphoma (PTCL)
- Lymphoblastic leukemia/lymphoma (less commonly derived from B cells)

### *Indolent B-cell NHLs include the following subtypes:*

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Follicular lymphoma (FL)
- Lymphoblastic leukemia/lymphoma (more commonly derived from T cells)
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (WM)
- Marginal zone lymphoma (MZL)

### *Indolent T-cell NHLs include the following subtypes:*

- Adult T-cell leukemia/lymphoma (ATLL)
- Cutaneous T-cell lymphoma (CTCL)
- Mycosis fungoides (MF)

## Treatment Options

A multitude of highly effective treatment options exist for patients with NHL, including:

- Chemotherapy (common treatments are bendamustine [Treanda] or CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone])
- Immunotherapy (includes the use of monoclonal antibodies, antibody-drug conjugates, radioimmunotherapy, immunomodulatory drugs, and chimeric antigen receptor [CAR] T-cell therapy)
- Targeted therapies
- Radiation therapy
- Stem cell transplantation
- *Active surveillance* (“watchful waiting,” approach in which no treatment is given, but patients are closely monitored)

The physician considers many factors when deciding the most appropriate form of treatment for each patient including the type and subtype of NHL; whether the lymphoma is *aggressive* (fast-growing) or *indolent* (slow-growing); the stage of the lymphoma; the patient’s symptoms (if any); prior therapies the patient received; the patient’s age and overall health (for example, other disease/conditions the patient may have); and the patient’s goals for treatment.

Sometimes after a patient has received an initial treatment, the disease may *relapse* (return after treatment) or become *refractory* (does not respond to treatment). However, numerous treatment options – often referred to as subsequent therapies – exist for patients with relapsed/refractory NHL. In fact, many of the new therapeutic agents that have been approved by the U.S. Food and Drug Administration, as well as many of those being investigated in clinical trials, focus specifically on treating patients with relapsed/refractory disease.

## Treatments Under Investigation

Many treatments at different stages of drug development are currently being tested in clinical trials for various subtypes of NHL. It is critical to remember that today’s scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.

## Clinical Trials

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF’s website at [www.lymphoma.org/publications](http://www.lymphoma.org/publications), talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

## Follow-up

Patients with lymphoma should have regular visits with a physician who is familiar with their medical history and the treatments they may have received. Medical tests (such as blood tests, CT scans, and PET scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term effects or late effects, which can vary based on duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any effects resulting from treatment or potential disease recurrences. LRF’s award-winning *Focus On Lymphoma* app ([www.FocusOnLymphoma.org](http://www.FocusOnLymphoma.org)) can help patients manage this documentation.

## Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts for people with lymphoma, as well as patient guides and e-Updates that provide the latest disease-specific news and treatment options.

## Patient and Caregiver Support Services

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. One-to-one peer support programs, such as LRF's *Lymphoma Support Network*, connects patients and caregivers with volunteers who have experience with lymphoma, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission.

### Patient Education

LRF offers a wide range of opportunities to learn about lymphoma.

*Ask the Doctor About Lymphoma* is a national series of two-hour, topic-specific, community-based programs that combine a presentation by a medical doctor with an extensive question-and-answer session.

*Lymphoma Workshops* are regional, full-day educational programs that provide the latest information about lymphoma, current treatment options, and patient support issues.

*The North American Educational Forum on Lymphoma* is held annually and provides critical information on treatment options, patient support issues, and the latest in lymphoma research.

*Webcasts* are available on specific types of lymphoma, treatment options, and support topics.

*Teleconferences* are hour-long, interactive telephone programs that provide an opportunity to learn more about lymphoma, treatments, and promising research from leading lymphoma experts.

### Patient Services and Support

The LRF Helpline staff members are available to answer your general questions about a lymphoma or CLL/SLL diagnosis and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter.

## Patient Publications

LRF offers a series of print and digital patient education publications. LRF offers comprehensive guides on non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and the transplantation process in lymphoma, along with a variety of disease- and topic-specific fact sheets. Contact the LRF Helpline at (800) 500-9976 or visit our website at [www.lymphoma.org/publications](http://www.lymphoma.org/publications).

### Mobile App

*Focus On Lymphoma* is the first mobile application (app) that provides patients and caregivers comprehensive content based on their lymphoma subtype and tools to help manage their disease such as, keep track of medications and blood work, track symptoms, and document treatment side effects. The *Focus On Lymphoma* mobile app is available for download for iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit [www.FocusOnLymphoma.org](http://www.FocusOnLymphoma.org).

To learn more about any of these resources, visit our website at [www.lymphoma.org](http://www.lymphoma.org), or contact the LRF Helpline at (800) 500-9976 or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

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