

Understanding Non-Hodgkin Lymphoma (Lymphoid Neoplasms)

Non-Hodgkin lymphoma (NHL) is the seventh 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. Currently, more than 74,000 new cases are diagnosed each year.

NHL is not a single cancer, but rather a group of several closely related cancers. The most recent 2016 revision of the World Health Organization (WHO) estimates that there are approximately 85 subtypes of NHL. Among these, three lymphoma subtypes make up the majority of NHLs in the United States. These are diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). 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* (click [here](#)) 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 T-cell lymphomas. B-cell lymphomas develop from abnormal B cells and account for about 90 percent of all NHLs. T-cell lymphomas develop from abnormal T cells and account for about 10 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 discussed and seen by a physician. Often however, the diagnosis is suggested as an incidental finding on a computed tomography (CT) scan done for other reasons or on screening mammograms, or found on routine physical exams.



DIAGNOSIS AND STAGING

A biopsy (a procedure that collects a sample of the tumor) of an affected lymph node is the only way to make a definite diagnosis of NHL. A *pathologist* (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples) and preferably a *hematopathologist* (pathologist who has undergone additional training in the diagnosis of blood cancers, 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 knowing the exact NHL subtype help identify appropriate treatment options to most effectively treat the patient's particular subtype of lymphoma.

Generally speaking, NHL is *systemic* (throughout the body). Staging is a process used to describe where the cancer is located and how widely the cancer has spread. The Lugano classification of the Ann Arbor staging system is used for most NHLs:

- stage I — disease is limited to 1 group of lymph nodes
- stage II — disease involves 2 or more lymph node groups, both either above or below, but just on one side of, the diaphragm (the muscle underneath your lungs)
- stage III — disease involves lymph node groups on both sides of the diaphragm
- stage IV — disease involves both lymph nodes and organs or bone marrow

To stage a lymphoma, the physician may order imaging tests such as abdominal and chest CT scans or a positron emission tomography (PET) scan. A CT scan allows the physician to see inside the chest and abdomen, locating the tumor. PET scans are a form of imaging that incorporates a special dye labeled to glucose (sugar) that tracks the metabolism of the lymphoma and relies upon the fact that tumor cells use sugar more than normal cells. Other staging tests may include a bone marrow biopsy, spinal tap, endoscopy/colonoscopy, and magnetic resonance imaging (MRI). Physicians may also request blood tests and an echocardiogram to help evaluate overall health.

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. People with a family history appear to be at slightly higher risk of developing lymphoma, often of the same subtype. Nonetheless, the likelihood of two first-degree relatives having lymphoma remains very small. In fact, most people with the known risk factors never develop NHL. 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's disease, rheumatoid arthritis, systemic lupus erythematosus, or psoriasis)
- Treatment for autoimmune diseases, especially with methotrexate and tumor necrosis factor-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 *Helicobacter pylori*, *Campylobacter jejuni*, or *Chlamydia psittaci*
- Older age — Like most cancers, NHL is much more common in adults older than 60 years, although it may develop in children and adults of all ages
- Males have slightly higher incidence rates of NHL than women
- Exposure to certain chemicals such as some herbicides (for example, Agent Orange) and pesticides, and some chemotherapy drugs used to treat other cancers
- 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 T cells) and how quickly the cancer grows (aggressive or indolent). Within each type of lymphoma 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. Knowing as much as possible about your lymphoma subtype, treatment options and their potential side effects can empower you to take charge of your health and better communicate with your physician. New research studies are defining different subsets that impact treatment decisions. The following list includes selected lymphoid malignancies in the current WHO classification.

AGGRESSIVE B-CELL NHLs INCLUDE THE FOLLOWING SUBTYPES:

- Burkitt lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- High-grade B-cell lymphoma, also known as double-hit lymphoma (DHL)
- Mantle cell lymphoma (MCL), sometimes classified as indolent

AGGRESSIVE T-CELL NHLs INCLUDE THE FOLLOWING SUBTYPES:

- Peripheral T-cell lymphoma (PTCL)
- Anaplastic large cell lymphoma (ALCL)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Adult T-cell leukemia/lymphoma (ATLL)

INDOLENT B-CELL NHLs INCLUDE THE FOLLOWING SUBTYPES:

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Follicular lymphoma (FL)
- Marginal zone lymphoma (MZL)
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (WM)

INDOLENT T-CELL NHLs INCLUDE THE FOLLOWING SUBTYPES:

- Cutaneous T-cell lymphoma (CTCL)
- Mycosis fungoides (MF)

TREATMENT OPTIONS

For patients with the indolent types of lymphoma who do not show any signs or symptoms an *active surveillance* approach may be taken. Active surveillance is also known as *watchful waiting* (observation with no treatment [drug therapy, radiation therapy, or stem cell transplantation] given) and the lymphoma is monitored with regular checkups. For patients with the aggressive types of lymphoma or those whose lymphoma begins to progress after a period of active surveillance, a multitude of highly effective treatment options exist for patients with NHL, including:

- Chemotherapy (common treatments are bendamustine 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



TREATMENTS UNDER INVESTIGATION

The physician considers many factors when deciding the most appropriate form of treatment, including the type and subtype of NHL; the stage of the lymphoma; the symptoms (if any); the prior therapies; the patient's age and overall health (for example, other conditions the patient may have); and the patient's goals for treatment.

Sometimes after an initial treatment, the lymphoma may *relapse* (returns after treatment) or become *refractory* (does not respond to treatment). However, numerous treatment options exist for patients with relapsed/refractory NHL.

Many treatments at different stages of drug development are currently being tested in clinical trials for various subtypes of NHL (Table 1). 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.

Table 1. Selected agents under investigation for NHL in Phase 2-3 clinical trials

AGENT	CLASS	UNDER INVESTIGATION FOR
Abexinostat (PCI-24781)	Targeted therapy; HDAC inhibitor	FL, DLBCL, MCL and NHL (subtype not specified)
ALLO-501A	CAR T cell; anti-CD19	Relapsed or refractory Large B cell lymphoma
APG-2575	Targeted therapy; Bcl-2 inhibitor	Relapsed or refractory CLL/SLL
AUT03	Dual target CAR T cell; anti-CD19 and CD22	Relapsed or refractory DLBCL
Blinatumomab (Blincyto)	Immunotherapy; bispecific antibody	DLBCL and other forms of B-cell NHL
DTRM-555	Targeted therapy; BTK inhibitor	Relapsed or refractory CLL/SLL, DLBCL and FL
Entospletinib (GS-9973)	Spleen tyrosine kinase inhibitor	CLL, FL, and other forms of NHL
Fimepinostat (CUDC-907)	Targeted therapy; dual PI3K and HDAC inhibitor	Relapsed and refractory lymphoma. Granted FDA Fast Track designation for adult patients with relapsed or refractory DLBCL
Iberdomide (CC-220)	Targeted therapy; cereblon E3 ligase modulator	FL and DLBCL
LNS8801	Targeted therapy; GPER agonist	NHL (subtype not specified)
MB-106	CAR T cell; anti-CD20	Relapsed or refractory NHL (subtype not specified)
Nanatinostat (VRx-3996)	Targeted therapy; HDAC inhibitor	Epstein-Barr Virus associated Lymphoma
Panobinostat (Farydak)	Targeted therapy; HDAC inhibitor	Relapsed/refractory NHL
Parsaclisib (INCB050465)	Targeted therapy; PI3K δ inhibitor	FL, MCL, relapsed or refractory DLBCL and CLL/SLL.
PBCAR0191	CAR T cell; anti-CD19	Relapsed or refractory NHL (subtype not specified)
PBCAR20A	CAR T cell; anti-CD20	Relapsed or refractory CLL/SLL and NHL (subtype not specified)

Table 1. Selected agents under investigation for NHL in Phase 2-3 clinical trials (continued)

AGENT	CLASS	UNDER INVESTIGATION FOR
Odronextamab	Immunotherapy; bispecific antibody	Relapsed or refractory B-cell NHL
Relmacabtagene autoleucl (Relma-cel, JWCAR029)	Autologous CAR T cell; anti-CD19	Relapsed or refractory DLBCL and FL
Tenalisib (RP6530)	Targeted therapy; PI3K δ/γ inhibitor	NHL and T cell lymphoma
Tislelizumab	Immune checkpoint inhibitor; anti-PD1	Relapsed or refractory B-cell lymphoma
Tolinapant (ASTX660)	Targeted therapy; IAP antagonist	Relapsed or refractory PTCL, CTCL and ATLL
Zandelisib (ME-401)	Targeted therapy; PI3K δ inhibitor	FL and MZL

Abbreviations: ATLL, adult T-cell leukemia lymphoma; Bcl-2, B-cell lymphoma 2; BTK, bruton tyrosine kinase; CAR, chimeric antigen receptor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FDA, food and drug administration; GPER, G protein-coupled estrogen receptor; FL, follicular lymphoma; HDAC, histone deacetylase; IAP, inhibitors of apoptosis proteins; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T cell lymphoma; PI3K, phosphoinositide 3-kinase; SLL, small lymphocytic lymphoma.



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 ([click here](#)), 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.



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 side 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 lymphoma 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 lymphoma recurrences. LRF's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) and Lymphoma Care Plan (lymphoma.org/publications) can help patients manage this documentation.



LRF'S HELPLINE AND LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. The LRF Helpline staff members are available to answer your general questions about a lymphoma 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. A part of the Helpline is LRF's one-to-one peer support programs, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with NHL, 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.



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 lymphoma 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 FocusOnLymphoma.org. To learn more about any of these resources, visit our website at lymphoma.org, or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and NHL. LRF also provides many educational activities, including our in-person meetings, podcasts, and webinars for people with lymphoma. For more information about any of these resources, visit our websites at lymphoma.org/NHL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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