LYMPHOMA RESEARCH • FOUNDATION

Understanding Lymphoma: 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 (US) nearly doubled between 1975 and 2013, while the rates have since stabilized. An estimate of 80,470 new cases of NHL will be diagnosed in the US in 2022.

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 US. These are diffuse large B-cell lymphoma (DBCL), 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* (**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 T-cell lymphomas. B-cell lymphomas develop from abnormal B cells and account for about 85% of all NHLs. T-cell lymphomas develop from abnormal T cells and account for less than 15% of all NHLs. NHL subtypes are also classified according to their growth pattern as *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 consult with a physician. Often the diagnosis is subsequent to an incidental finding on a routine medical checkup or on exams done for other reasons, like a computed tomography (CT) scan or a screening mammogram.

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. Excisional biopsies where an entire lymph node or tumor is removed are preferred to needle biopsies when making a diagnosis of lymphoma to ensure there is sufficient tissue present to determine the type of lymphoma. 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 knowledge of the exact NHL subtype helps identify appropriate treatment options for the patient's particular subtype of NHL.

After a diagnosis of NHL, it is important to determine if and how far the lymphoma has spread. This process is called *staging*, and helps to determine the severity of the disease and the appropriate treatment. 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, but just on one side (either above or below) of the diaphragm (the muscle underneath your lungs)
- **stage III** – disease involves lymph node groups on both sides of the diaphragm (above and below.
- **stage IV** – disease involves 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. A PET scan is a form of imaging that incorporates a special dye that tracks the metabolism of the lymphoma 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 and risks with chemotherapy.

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, ataxia-telangiectasia or Wiskott-Aldrich syndrome) or infection with human immunodeficiency virus (HIV)
- 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], human herpes virus 8 [HHV-8], 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 (benzene), herbicides (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). 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. The following list includes selected lymphoid malignancies in the current WHO classification. This list includes chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), which are different forms of the same disease.

AGGRESSIVE B-CELL NHLS INCLUDE THE FOLLOWING SUBTYPES:

- Burkitt lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Primary Mediastinal B-cell lymphoma
- 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), including 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 aggressive NHL, or those whose lymphoma begins to progress after a period of active surveillance, several highly effective treatment options exist, including:

- Chemotherapy (common treatments are bendamustine or CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone])
- Immunotherapy (includes the use of monoclonal antibodies like rituximab (Rituxan), bispecific antibodies, antibody-drug conjugates, immunomodulatory drugs, and chimeric antigen receptor [CAR] T-cell therapy)
- Targeted therapies
- Radiation therapy
- Stem cell transplantation

The physician considers many factors when deciding the most appropriate form of treatment, including type and subtype of NHL; disease stage; symptoms (if any); prior therapies; 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.

TREATMENTS UNDER INVESTIGATION

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 scientific research is continuously evolving and 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
AB-205 (E-CEL cells)	**Cell therapy; RMAT**	• NHL (subtype not specified)
Abexinostat (PCI-24781)	**Targeted therapy; HDAC inhibitor**	• NHL (subtype not specified)
ALLO-501A	**CAR T cell; anti-CD19**	• Relapsed or refractory Large B cell lymphoma
AUTO3	**Dual target CAR T cell; anti-CD19 and CD22**	• Relapsed or refractory DLBCL
DTRM-555	**Targeted therapy; BTK inhibitor**	• Relapsed or refractory CLL/SLL, DLBCL and FL
GC022F	**CAR T cell; anti-CD19 and CD-22**	• Recurrent or refractory B-cell NHL
Iberdomide (CC-220)	**Targeted therapy; cereblon E3 ligase modulator**	• FL and DLBCL
LNS8801	**Targeted therapy; GPER agonist**	• NHL (subtype not specified)
Mosunetuzumab (BTCT4465A)	**Immunotherapy; bispecific antibody**	• B-cell NHL
Nanatinostat (VRx-3996)	**Targeted therapy; HDAC inhibitor**	• Epstein-Barr Virus associated Lymphoma
Parsaclisib (INCB050465)	**Targeted therapy; PI3Kδ inhibitor**	• FL, MZL, 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)
Odronextamab	**Immunotherapy; bispecific antibody**	• Relapsed or refractory B-cell NHL
Orelabrutinib (ICP-022)	**Targeted therapy; BTK inhibitor**	• Relapsed or refractory B-cell NHL, MCL
Relmacabtagene autoleucel (Relma-cel, JWCAR029)	**Autologous CAR T cell; anti-CD19**	• Relapsed or refractory DLBCL and FL

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

Agent	Class	Under investigation for
Tislelizumab)	**Immune checkpoint inhibitor; anti-PD-1**	• Relapsed or refractory B-cell lymphoma
Tolinapant (ASTX660)	**Targeted therapy; IAP antagonist**	• Relapsed or refractory PTCL, CTCL and ATLL
Ublituximab (TG-1101)	**Immunotherapy; anti-CD20**	• NHL (subtype not specified)
Zandelisib (ME-401)	**Targeted therapy; PI3Kδ inhibitor**	• FL and MZL

Abbreviations: ATLL, adult T-cell leukemia lymphoma; 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; FL, follicular lymphoma; GPER, G protein-coupled estrogen receptor; HDAC, histone deacetylase; IAP, inhibitors of apoptosis proteins; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PD-1, programmed cell death protein 1; PTCL, peripheral T cell lymphoma; PI3K, phosphoinositide 3-kinase; RMAT, regenerative medicine advanced therapy; 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 (**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**.

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, including NHL, 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**.

LYMPHOMA CARE PLAN

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. LRF offers a Lymphoma Care Plan as a resource for patients and their caregivers. LRF's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting **lymphoma.org/publications**.

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, 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**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**.)

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