Non-Hodgkin lymphoma (NHL) is among the seven most common cancers affecting adults in the U.S. The number of new cases of NHL in the US nearly doubled between 1975 and 2013 but have since remained stable. An estimate of 80,550 new cases of NHL will be diagnosed in the US by the end of 2023.

NHL is not a single cancer, but rather a group of closely related cancers. NHL is a type of blood cancer that affects the white blood cells called lymphocytes. Lymphocytes work together with other cells in the immune system to help the body fight infections and other diseases. 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:

- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma (FL)
- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

The various types of NHL share many common factors, but they differ in certain characteristics like:

- How they look under a microscope
- How they grow and spread in the body
- How they respond to treatment

NHLs are categorized as B-cell NHL or T-cell NHL, according to the type of white blood cell affected, and as indolent (slow-growing) or aggressive (fast-growing), according to how fast they grow in the body.

Common signs and symptoms of NHL may include:

- Swelling of the lymph nodes (usually painless)
- Fever
- Night sweats
- Unexplained weight loss
- 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. The disease is sometimes diagnosed after a routine medical checkup or exams done for other reasons, like a computed tomography (CT) scan or a screening mammogram.

For more in-depth information on NHL, please see the Lymphoma Research Foundation’s (LRF’s) guide *Understanding Lymphoma* (lymphoma.org/publications) or call the LRF Lymphoma Helpline at 800-500-9976 to order a copy.
After a diagnosis of NHL, it is important to determine if, and how far, the lymphoma has spread. This process is called staging, and it uses the results of the different tests (such as biopsies and scans) to determine the severity of the disease and the appropriate treatment. The Lugano staging classification is used for most NHLs (except CLL/SLL) and is depicted in Figure 1 below. This system categorizes NHL from stage I (least severe) to stage IV (most severe), based on whether the disease is restricted to a single group of lymph nodes, has spread to other lymph nodes, or has reached the bone marrow (the spongy tissue inside the bones) and/or other organs (like the liver or lungs).

**RISK FACTORS**

The characteristics that may make a person more at risk of developing any type of disease are called risk factors. Having one or more risk factors for NHL does not mean a person will develop NHL. People with a family history of NHL appear to be at slightly higher risk of developing the disease, often the same subtype. Nonetheless, the likelihood of two first-degree relatives having NHL remains very small. In fact, most people with the known risk factors never develop NHL. The causes of NHL in most cases remain unknown. 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 (the body’s immune system attacks its own healthy cells). For example, Crohn’s disease, rheumatoid arthritis, systemic lupus erythematosus, or psoriasis
- Treatment for autoimmune diseases, especially with methotrexate and drugs that target a protein called tumor necrosis factor
- Treatment with certain drugs used after organ transplantation
- Infection with certain viruses (for example, Epstein-Barr virus [EBV], human T-cell lymphotropic virus type 1 [HTLV-1], human herpes virus type 8 [HHV-8], or hepatitis C virus [HCV])
- Infection with the bacteria Helicobacter pylori, Campylobacter jejuni, or Chlamydia psittaci
- Older age (NHL is much more common in adults older than 60 years, although it may develop in children and adults of all ages.)
- Male (a slightly higher number of new cases of NHL than women)
- Exposure to certain chemicals (like benzene), herbicides (like Agent Orange) and pesticides, and some chemotherapy drugs used to treat other cancers
- Treatment with radiation therapy for other cancers or previous NHL

**TYPES AND SUBTYPES OF NHL**

The classification of NHL is complicated and has evolved over the years. NHL subtypes are grouped according to which kind of white blood cell 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. By knowing as much as possible about your NHL 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 table includes blood diseases in the current WHO classification. This table includes chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), which are different forms of the same disease.

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**Figure 1.** Staging of NHL, according to the Lugano classification. NHL, non-Hodgkin lymphoma.

To stage a lymphoma, the patient might need 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 uses a special dye to locate the lymphoma cells in the body. Other staging tests may include a bone marrow biopsy, spinal tap (lumbar puncture; a procedure where a small needle is inserted into the back and spinal fluid is withdrawn), endoscopy/colonoscopy (medical procedures where an instrument is introduced into the body to give a view of the stomach or colon, respectively), and magnetic resonance imaging (MRI; a type of scan that uses a strong magnet and radio waves to produce detailed images of the inside of the body). Physicians may also request blood tests and an echocardiogram (a type of scan that uses sound waves to produce images of the heart and nearby blood vessels) to help evaluate overall health and risks with chemotherapy.
Table 1. Types of NHL by Cell Type and Growth Pattern

<table>
<thead>
<tr>
<th>Aggressive</th>
<th>Indolent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell NHL</strong></td>
<td><strong>T-cell NHL</strong></td>
</tr>
<tr>
<td>• Burkitt lymphoma</td>
<td>• Peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>• Diffuse large B-cell lymphoma</td>
<td>• Anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>• Primary mediastinal B-cell lymphoma</td>
<td>• Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>• High-grade B-cell lymphoma</td>
<td>• Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>• Mantle cell lymphoma</td>
<td>• Sézary syndrome</td>
</tr>
</tbody>
</table>

NHL, non-Hodgkin lymphoma.

The figures below shows how common or uncommon B- and T-cell NHLs are.

**Figure 2.** Relative frequencies of B-cell NHL in the U.S. Percentages are based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data, 2008-2017. SEER Program provides information on cancer statistics. Some very rare types are not shown in the graph. NHL, non-Hodgkin lymphoma.

**Figure 3.** Relative frequencies of T-cell NHL in the U.S. Percentages are based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data, 2008-2017. Some very rare types are not shown in the graph. NHL, non-Hodgkin lymphoma.
TREATMENT OPTIONS

For patients with the indolent types of NHL who do not show any signs or symptoms, an active surveillance approach (observation with no treatment given) may be taken. Active surveillance is also known as watchful waiting and the disease is watched with regular checkups. For patients with aggressive NHL, or those whose lymphoma begins to progress (grow and/or spread) after a period of active surveillance, several highly effective treatment options exist. The most common therapy categories include:

- **Chemotherapy** (drugs that stop the growth of or kill cancer cells). Common chemotherapy drugs are bendamustine [Treanda] or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).
- **Immunotherapy** (drugs that use the body’s immune system to fight cancer). This 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** (drugs that target molecules that cancer cells use to grow and spread). This includes inhibitors of proteins involved in cell signaling and growth-like kinases and other proteins.
- **Radiation therapy** (uses high-energy radiation to kill cancer cells).
- **Stem cell transplantation** (The patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells, or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow’s ability to make new blood cells.)

A combination of these drugs is often used to treat NHLs, such as chemoimmunotherapy. In this case, chemotherapy is paired with immunotherapy (such as the combination bendamustine [Treanda] and rituximab [Rituxan]). Patients seeking information about targeted therapy and immunotherapy should view the Understanding Immunotherapy and Lymphoma fact sheet on LRF’s website [lymphoma.org/publications].

The physician considers many factors when deciding the most appropriate form of treatment, including the 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 (return after treatment) or become refractory (does not respond to treatment). However, there are many treatment options that may be available to someone who has relapsed or is refractory to their last treatment. It is important to talk to your doctor about the available treatment options.

TREATMENTS UNDER INVESTIGATION

Various treatments for different subtypes of NHL, and at different stages, are currently being investigated in clinical trials (Table 2).

It is critical to remember that scientific research is always 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. For a complete list of clinical trials in NHL, visit [https://clinicaltrials.gov/](https://clinicaltrials.gov/).

<table>
<thead>
<tr>
<th>Agent (Drug)</th>
<th>Class (Type of Treatment)</th>
<th>Under Investigation for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abexinostat (PCI-24781)</td>
<td>Targeted therapy; HDAC inhibitor</td>
<td>NHL (subtype not specified), FL, DLBCL, MCL</td>
</tr>
<tr>
<td>ALLO-501A</td>
<td>CAR T-cell; anti-CD19</td>
<td>Relapsed or refractory large B-cell lymphoma</td>
</tr>
<tr>
<td>AUTO3</td>
<td>Dual target CAR T-cell; anti-CD19 and CD22</td>
<td>Relapsed or refractory DLBCL</td>
</tr>
<tr>
<td>DTRM-555</td>
<td>Targeted therapy; BTK inhibitor</td>
<td>Relapsed or refractory CLL/SLL, DLBCL, and FL</td>
</tr>
<tr>
<td>GC022F</td>
<td>CAR T-cell; anti-CD19 and CD-22</td>
<td>Recurrent or refractory B-cell NHL</td>
</tr>
<tr>
<td>Iberdomide (CC-220)</td>
<td>Targeted therapy; cereblon E3 ligase modulator</td>
<td>FL and DLBCL</td>
</tr>
<tr>
<td>Isatuximab</td>
<td>Immunotherapy; anti-CD38</td>
<td>Relapsed DLBCL, MCL, PTCL</td>
</tr>
<tr>
<td>Nanatinostat (VRx-3996)</td>
<td>Targeted therapy; HDAC inhibitor</td>
<td>Epstein-Barr virus-associated lymphoma</td>
</tr>
<tr>
<td>Parsaclisib</td>
<td>Targeted therapy; PI3Kδ inhibitor</td>
<td>FL, MZL, MCL, relapsed or refractory DLBCL and CLL/SLL</td>
</tr>
<tr>
<td>PBCAR0191</td>
<td>CAR T-cell; anti-CD19</td>
<td>Relapsed or refractory NHL (subtype not specified)</td>
</tr>
<tr>
<td>Odronextamab</td>
<td>Immunotherapy; bispecific antibody</td>
<td>Relapsed or refractory B-cell NHL</td>
</tr>
</tbody>
</table>
Table 2. Selected Agents Under Investigation for DLBCL in Phase 2-3 Clinical Trials

<table>
<thead>
<tr>
<th>Agent (Drug)</th>
<th>Class (Type of Treatment)</th>
<th>Disease Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orelabrutinib (ICP-022)</td>
<td>Targeted therapy; BTK inhibitor</td>
<td>Relapsed or refractory B-cell NHL, MCL</td>
</tr>
<tr>
<td>Relmacabtagene autoleucel</td>
<td>Autologous CAR T-cell; anti-CD19</td>
<td>Relapsed or refractory DLBCL, MCL, and FL</td>
</tr>
<tr>
<td>(relma-cel, JWCAR029)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAK-007</td>
<td>CAR NK cells; anti-CD19</td>
<td>Relapsed or refractory B-cell NHL</td>
</tr>
<tr>
<td>Tislelizumab</td>
<td>Immune checkpoint inhibitor; anti-PD-1</td>
<td>Relapsed or refractory B- and T-cell lymphoma</td>
</tr>
<tr>
<td>Tolinapant (ASTX660)</td>
<td>Targeted therapy; IAP antagonist</td>
<td>Relapsed or refractory PTCL</td>
</tr>
</tbody>
</table>

Abbreviations: BTK, Bruton’s tyrosine kinase; CAR, chimeric antigen receptor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic 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; NK, natural killer; PD-1, programmed cell death protein 1; PTCL, peripheral T-cell lymphoma; PI3K, phosphoinositide 3-kinase; SLL, small lymphocytic lymphoma.

**CLINICAL TRIALS**

Clinical trials are crucial in identifying effective drugs and the best treatment doses for patients with relapsed or refractory MCL. Because the optimal initial treatment of MCL is not clear and it is such a rare disease, clinical trial enrollment is important for establishing more-effective and less-toxic treatments. The rarity of the disease also means that the latest treatments are often available only through clinical trials. Patients interested in participating in a clinical trial should view the [Understanding Clinical Trials](lymphoma.org/publications) fact sheet on LRF’s website, 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 their physician. 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 side effects (occur during treatment and continue for months or years) or late side effects (appear only months, years, or decades after treatment has ended), 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. These include test results as well as information on the type, amount, and duration of all treatments received. Medical records are important for keeping track of any side 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.

**LYMPHOMA CARE PLAN AND PATIENT EDUCATION PROGRAMS**

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’s [Lymphoma Care Plan](lymphoma.org/publications) fact sheet 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](lymphoma.org/publications) fact sheet can be accessed by visiting lymphoma.org/publications. LRF also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit lymphoma.org/programs.
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LRF FOCUS ON LYMPHOMA MOBILE APP

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