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### **About Non-Hodgkin Lymphoma**

Get an overview of non-Hodgkin lymphoma and the latest key statistics in the US.

#### **Overview and Types**

If you have been diagnosed with non-Hodgkin lymphoma or are worried about it, you likely have a lot of questions. Learning some basics is a good place to start.

- What Is Non-Hodgkin Lymphoma?
- Types of B-cell Lymphoma
- Types of T-cell Lymphoma

#### **Research and Statistics**

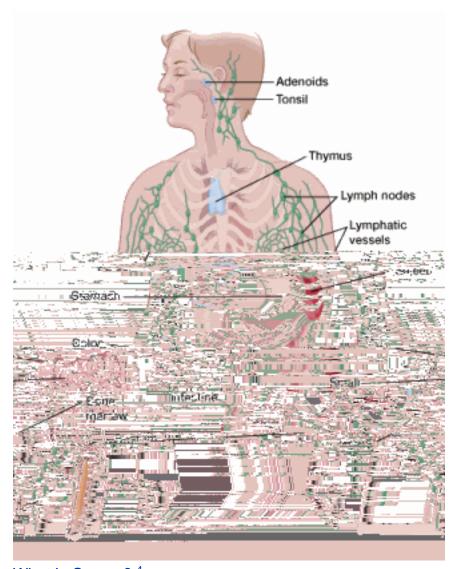
See the latest estimates for new cases of non-Hodgkin lymphoma and deaths in the US and what research is currently being done.

- Key Statistics for Non-Hodgkin Lymphoma
- What's New in Non-Hodgkin Lymphoma Research and Treatment?

# What Is Non-Hodgkin Lymphoma?

**Non-Hodgkin lymphoma** (also known as **non-Hodgkin's lymphoma**, **NHL**, or sometimes just **lymphoma**) is a cancer that starts in white blood cells called **lymphocytes**, which are part of the body's immune system.

NHL is a term that's used for many different types of lymphoma that all share some of the same traits. There is another main type of lymphoma, called



#### What Is Cancer? 4

Cancer starts when cells in the body begin to grow out of control. Cells in nearly any part of the body can become cancer cells. Learn more here.

Lymphatic System

#### Anatomy Gallery: Lymphatic System <sup>5</sup>

Explore our 3D interactive tour of the lymphatic system.

#### Types of non-Hodgkin lymphoma

Treatment for NHL depends on which type it is, so it's important for doctors to find out the exact type of lymphoma you have. The type of lymphoma depends on what type of

lymphocyte is affected (B cells or T cells), how mature the cells are when they become cancerous, and other factors.

#### **B-cell versus T-cell lymphomas**

The lymph system is made up mainly of lymphocytes, a type of white blood cell that helps the body fight infections. There are 2 main types of lymphocytes:

- B lymphocytes (B cells): B cells normally help protect the body against germs (bacteria or viruses) by making proteins called antibodies. The antibodies attach to the germs, marking them for destruction by other parts of the immune system.
- T lymphocytes (T cells): There are several types of T cells. Some T cells destroy germs or abnormal cells in the body. Other T cells help boost or slow the activity of other immune system cells.

Lymphoma can start in either type of lymphocytes, but B-cell lymphomas are most common.

#### **Indolent versus aggressive lymphomas**

Types of NHL can also be grouped based on how fast they grow and spread:

- **Indolent lymphomas** grow and spread slowly. Some indolent lymphomas might not need to be treated right away but can be watched closely instead. The most common type of indolent lymphoma in the United States is follicular lymphoma.
- Aggressive lymphomas grow and spread quickly. They usually need to be treated right away. The most common type of aggressive lymphoma in the United States is diffuse large B cell lymphoma (DLBCL).
- Some types of lymphoma, like mantle cell lymphoma, don't fit neatly into either of these groups.

Regardless of how quickly they grow, all non-Hodgkin lymphomas can spread to other parts of the lymph system if not treated. Eventually, they can also spread to other parts of the body, such as the liver, brain, or bone marrow.

#### Classifying types of NHL



B-cell lymphomas make up most (about 85%) of the non-Hodgkin lymphomas (NHL) in the United States. These types of lymphomas start in early forms of B lymphocytes (B cells). The most common types of B-cell lymphomas are listed below.

#### Follicular lymphoma

About 1 out of 5 lymphomas in the United States is a follicular lymphoma. This is usually a slow-growing (indolent) lymphoma, although some follicular lymphomas can grow quickly.

The average age for people with this lymphoma is about 60. It's rare in very young people. This lymphoma usually occurs in many lymph node sites in the body. It can also occur in the bone marrow.

Follicular lymphomas often respond well to treatment, but they are hard to cure. These lymphomas may not need to be treated when they are first diagnosed. Often, treatment may be delayed until the lymphoma starts causing problems. Over time, some follicular lymphomas can turn into a fast-growing diffuse large B-cell lymphoma.

# Chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL)

CLL and SLL are closely related diseases. In fact, many doctors consider them different versions of the same disease. The same type of cancer cell (known as a **small lymphocyte**) is seen in both CLL and SLL. The only difference is where the cancer cells are found. In CLL, most of the cancer cells are in the blood and bone marrow. In SLL, the cancer cells are mainly in the lymph nodes and spleen.

Both CLL and SLL are usually slow-growing (indolent) lymphomas, although CLL, which is much more common, tends to grow more slowly. Treatment is the same for CLL and SLL. These lymphomas are usually not curable, but because they tend to grow slowly, they often don't need to be treated when they are first found. Treatment can often be very helpful when it's needed, and many people can live a long time (even decades) with CLL or SLL.

Sometimes, these lymphomas can turn into a more aggressive (fast-growing) type of lymphoma over time.

To learn more, see Chronic Lymphocytic Leukemia<sup>1</sup>.

#### Mantle cell lymphoma (MCL)

About 5% of lymphomas are mantle cell lymphomas. MCL is much more common in men than in women, and it most often appears in people older than 60. When MCL is

diagnosed, it is usually widespread in the lymph nodes, bone marrow, and often the spleen.

MCL can be hard to treat. It tends to grow faster than indolent (slow-growing) lymphomas, but it doesn't usually respond to treatment as well as aggressive (fast-growing) lymphomas. Newer treatments might offer a better chance for long-term survival for people being diagnosed with MCL.

#### Marginal zone lymphomas

Marginal zone lymphomas account for about 5% to 10% of lymphomas. They tend to be slow growing (indolent). The cells in these lymphomas look small under the microscope. There are 3 main types of marginal zone lymphomas:

Extranodal marginal zone B-cell lymphoma, also known as mucosa-associated lymphoid tissue (MALT) lymphoma: This is the most common type of marginal zone lymphoma. It starts in places other than the lymph nodes (extranodal sites).

There are gastric and non-gastric MALT lymphomas:

- **Gastric MALT lymphomas** start in the stomach and are linked to infection with *Helicobacter pylori* (*H. pylori*), the bacteria that causes many stomach ulcers.
- Non-gastric MALT lymphomas start outside the stomach, such as in the lungs, skin, thyroid, salivary glands, or tissues around the eye. The lymphoma usually stays in the area where it begins and doesn't spread. Many of these lymphomas have also been linked to infections with bacteria or viruses.

The average age of people with MALT lymphoma at the time of diagnosis is about 66. This lymphoma tends to grow slowly and is often curable if the cancer is not advanced.

**Nodal marginal zone B-cell lymphoma:** This is a rare type of lymphoma. It starts and usually stays in the lymph nodes, although lymphoma cells can sometimes be found in the bone marrow.

This lymphoma tends to be slow growing (although not usually as slow as MALT lymphoma), and it's treated similarly to follicular lymphoma.

**Splenic marginal zone B-cell lymphoma:** This is a rare lymphoma. Often the lymphoma is found mainly in the spleen, blood, and bone marrow.

It can cause tiredness and discomfort due to an enlarged spleen. Because the disease is slow growing, it might not need to be treated unless the symptoms become troublesome. This type of lymphoma has been linked to hepatitis C infection. Treatment for the hepatitis C virus is discussed in detail in <a href="Irreating B-cell Non-Hodgkin Lymphoma">Irreating B-cell Non-Hodgkin Lymphoma</a>

nodes, and spleen.	This lymphoma is discussed in detail in	
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have immune system problems that may be due to <u>AIDS</u><sup>5</sup> or anti-rejection drugs after an organ or tissue transplant.

People may notice bulging of the eyeball without pain, vision loss, or blurry vision. Many of the <u>tests done to diagnose ocular melanoma</u><sup>6</sup> are the same used to diagnose lymphoma of the eye.

The main <u>treatment for lymphoma of the eye</u><sup>7</sup> is external radiation therapy if the cancer is limited to the eye. Chemotherapy (chemo) or chemotherapy in combination with radiation may be used depending on the type of lymphoma and how far it has spread outside of the eye.

#### **Hyperlinks**

- 1. www.cancer.org/cancer/types/chronic-lymphocytic-leukemia.html
- 2. <u>www.cancer.org/cancer/types/non-hodgkin-lymphoma/treating/b-cell-lymphoma.html</u>
- 3. www.cancer.org/cancer/types/waldenstrom-macroglobulinemia.html
- 4. www.cancer.org/cancer/types/chronic-lymphocytic-leukemia.html
- 5. www.cancer.org/cancer/risk-prevention/infections/hiv-infection-aids.html
- 6. www.cancer.org/cancer/types/eye-cancer/detection-diagnosis-staging/tests.html
- 7. <u>www.cancer.org/cancer/types/non-hodgkin-lymphoma/treating/b-cell-lymphoma.html</u>

#### References

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## **Types of T-cell Lymphoma**

T-cell lymphomas make up less than 15% of non-Hodgkin lymphomas in the United States. These lymphomas start in early forms of T lymphocytes (T cells). There are many types of T-cell lymphoma, but they are all fairly rare.

- T-lymphoblastic lymphoma/leukemia
- Peripheral T-cell lymphomas

#### T-lymphoblastic lymphoma/leukemia

Lymphoblastic lymphoma/leukemia (also known as **T cell acute lymphoblastic leukemia/lymphoma**) accounts for about 1% of all lymphomas. It's most common in teens or young adults, with males being affected more often than females. It can be thought of as either a lymphoblastic lymphoma (LBL) or a type of acute lymphoblastic leukemia (ALL), depending on how much of the bone marrow is involved (leukemias have more cancer cells in the bone marrow). The cancer cells are very early forms of T cells.

This lymphoma often starts in the thymus (a small organ behind the breastbone and in front of the heart, which is where many T cells are made) and can grow into a large tumor in the mediastinum (the area between the lungs). This can cause trouble breathing and swelling in the arms and face.

This lymphoma is fast-growing, but there is a good chance of curing it with

lymphomas. To learn more, see <u>Lymphoma of the Skin</u><sup>2</sup>.

**Adult T-cell leukemia/lymphoma**: This lymphoma is caused by infection with a virus called *HTLV-1*. It is rare in the United States, and much more common in Japan, the Caribbean, and parts of Africa – where infection with HTLV-1 is more common. It can affect the bone marrow (where new blood cells are made), lymph nodes, spleen, liver, skin, and other organs. There are 4 subtypes:

- The **smoldering** subtype tends to grow slowly. It often has no symptoms, and it tends to have a good prognosis (outlook).
- The **chronic** subtype also grows slowly and tends to have a good prognosis.
- The **acute** subtype is the most common. It grows quickly like acute leukemia, so it needs to be treated right away.
- The **lymphoma** subtype grows more quickly than the chronic and smoldering types, but not as fast as the acute type.

Angioimmunoblastic T-cell lymphoma (AITL): This lymphoma accounts for about 4% of all lymphomas. It is more common in older adults. It tends to involve the lymph nodes and bone marrow, as well as the spleen or liver, which can become enlarged. People with this lymphoma usually have fever, weight loss, skin rashes, and often develop 87 155.70 oi lymphoma of518 the 9.55lin 0 .62745 rinte6tinepes:87 141.not as fast as th519482 gp0 0

Monomorphic epitheliotropic intestinal T cell lymphoma (MEITL): This rare type of lymphoma also affects the lining of the intestines, but it is not linked to celiac disease.

Anaplastic large cell lymphoma (ALCL): About 2% of lymphomas are of this type. It is more common in young people (including children), but it can also affect older adults. This type of lymphoma tends to be fast growing, but many people with this lymphoma can be cured.

There are different forms of ALCL:

- **Primary cutaneous ALCL** only affects the skin. This is discussed in more detail in Lymphoma of the Skin<sup>3</sup>.
- Systemic ALCL can affect the lymph nodes and other organs, including the skin. Systemic ALCL is divided into 2 types based on whether the lymphoma cells have a change in the ALK gene. *ALK-positive* ALCL is more common in younger people and tends to have a better prognosis (outlook) than the *ALK-negative* type.
- Breast implant-associated ALCL is a rare type of ALCL that can develop in the breasts of women who have had implants. It seems to be more likely to happen if the implant surfaces are textured (as opposed to smooth).

**Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS):** This name is given to T-cell lymphomas that don't fit well into any of the groups above. Most people diagnosed 0 rg /Aise.62745 RG 0.75 6 the

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# **Key Statistics for Non-Hodgkin Lymphoma**

Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States, accounting for about 4% of all cancers.

The American Cancer Society's estimates for non-Hodgkin lymphoma in 2024 are:

- About 80,620 people (44,590 males and 36,030 females) will be diagnosed with NHL. This includes both adults and children.
- About 20,140 people will die from this cancer (11,780 males and 8,360 females).

Overall, the chance that a man will develop NHL in his lifetime is about 1 in 42; for a woman, the risk is about 1 in 52. But each person's risk can be affected by a number of risk factors<sup>1</sup>.

NHL can occur at any age. In fact, it is one of the more common cancers among <a href="mailto:children">children</a>2, <a href="teens">teens</a>3, and <a href="young adults">young adults</a>4. Still, the risk of developing NHL increases throughout life, and more than half of people are 65 or older when they are first diagnosed.

Incidence rates have declined by about 1% per year for NHL since 2015. And from 2012 to 2021, the death rate decreased by 2% per year.

#### **Hyperlinks**

- 1. <u>www.cancer.org/cancer/types/non-hodgkin-lymphoma/causes-risks-prevention/risk-factors.html</u>
- 2. www.cancer.org/cancer/types/cancer-in-children.html
- 3. www.cancer.org/cancer/types/cancer-in-adolescents.html
- 4. www.cancer.org/cancer/types/cancer-in-young-adults.html

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American Cancer Society. *Cancer Facts & Figures 2024*. Atlanta: American Cancer Society; 2024.

Freedman AS, Jacobson CA, Mauch P, Aster JC. Chapter 103: Non-Hodgkin's lymphoma. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology.* 10th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2015.

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# What's New in Non-Hodgkin Lymphoma Research and Treatment?

Research into the causes, prevention, and treatment of non-Hodgkin lymphoma (NHL) is being done in many medical centers throughout the world.

- Genetics
- Treatment

#### **Genetics**

Scientists are making a lot of progress in understanding how changes in the DNA inside normal lymphocytes can cause them to develop into lymphoma cells. Once this is understood, medicines may be developed that block these processes.

Progress in understanding DNA changes in lymphoma cells has already led to improved tests for detecting this disease. Some of these tests are already in use, and others are being developed. They may be used to:

- Detect lymphoma cells in a biopsy sample
- Determine what type of lymphoma a person has
- Help determine if a lymphoma is likely to grow and spread, even within a certain subtype of lymphoma
- Help figure out if a certain treatment is likely to be helpful
- Help determine if a lymphoma has been destroyed by treatment or if a relapse is likely

For example, in recent years, genetic tests have shown that there are different subtypes of diffuse large B-cell lymphoma (DLBCL), even though they look the same under the microscope. These subtypes seem to have different outlooks (prognoses) and responses to treatment. The hope is that such tests can be used to help guide treatment decisions.

#### **Treatment**

Much of the research being done on NHL is focused on looking at new and better ways to treat this disease.

#### Chemotherapy

Many new chemotherapy drugs are being studied in <u>clinical trials</u><sup>1</sup>. These studies have led to the approval of medicines such as bendamustine (Treanda) and pralatrexate

(Folotyn) for use against certain types of lymphoma. Other studies are looking at new ways to combine chemo drugs, either with each other or with other types of cancer medicines.

#### Stem cell transplants

Researchers continue to improve <u>stem cell transplant</u><sup>2</sup> methods, including new ways to collect the stem cells before the transplant.

Autologous transplants (which use the patient's own stem cells rather than cells from a donor) have the risk of reintroducing lymphoma cells back into the patient after treatment. Researchers are testing new and improved ways to separate out the last traces of lymphoma cells from the stem cells before they are returned to the patient. Some of the new monoclonal antibodies developed for treating lymphoma may help remove these remaining cells.

Researchers are also studying the effectiveness of non-myeloablative (reducedintensity) stem cell transplants in people with lymphoma. This approach may allow more people to benefit from stem cell transplants, especially those who are older or in poor health.

#### **Targeted drug therapies**

As researchers have learned more about lymphoma cells, they have developed newer medicines that target specific parts of these cells. These targeted drugs are different from standard chemotherapy drugs, which work by attacking rapidly growing cells. Targeted drugs may work in some cases where chemotherapy doesn't, and they often have different side effects.

Some <u>targeted drugs</u><sup>3</sup> are already being used to treat some types of NHL, and are being studied for use against other types.

Many other targeted drugs are now being studied in clinical trials.

#### **Immunotherapy**

Doctors have known for some time that people's immune systems may help fight their cancer. Scientists are now trying to develop ways to encourage this immune reaction. Some types of immunotherapy are already being used to treat lymphoma, as discussed in Immunotherapy for Non-Hodgkin Lymphoma<sup>4</sup>.

**Monoclonal antibodies:** Lymphoma cells have certain proteins on their surface. Monoclonal antibodies can be made to target these proteins and destroy the lymphoma cells while causing little damage to normal body tissues. This treatment strategy has already proven effective. Several such drugs, including rituximab (Rituxan), are already used to treat lymphoma.

Some newer antibodies are attached to substances that can poison cancer cells. These are known as **antibody-drug conjugates (ADCs)**. They act as homing devices to deliver the toxins directly to the cancer cells. For example:

- Brentuximab vedotin (Adcetris) is made up of an antibody to CD30 that is attached to a cell poison. It has been shown to help treat people with anaplastic large cell lymphoma (ALCL) and is now being studied for use against other types of lymphoma.
- **Moxetumomab pasudotox** targets the CD22 antigen on certain lymphoma cells, bringing along a toxin known as PE38. It's being used in clinical trials to treat hairy cell leukemia (HCL).

Other ADCs are now being studied as well.

**Immune checkpoint inhibitors:** Immune system cells normally have proteins that act as checkpoints to keep them from attacking other healthy cells. Cancer cells sometimes take advantage of these checkpoint proteins to avoid being attacked by the immune system. Some newer medicines, such as pembrolizumab (Keytruda) and nivolumab (Opdivo), work by blocking these checkpoints, which can boost the immune response against cancer cells. These drugs have shown promise in treating several types of cancer and are now being studied for use against some types of lymphoma.

Chimeric antigen receptor (CAR) T-cell therapy: In this treatment, immune cells called T cells are removed from the patient's blood and altered in the lab to have specific receptors (called chimeric antigen receptors, or CARs) on their surface. These receptors can attach to proteins on the surface of lymphoma cells. The T cells are then multiplied in the lab and given back into the patient's blood, where they can seek out the lymphoma cells and launch a precise immune attack against them.

This technique has shown encouraging results in early clinical trials against some hard-to-treat lymphomas. Doctors are still improving how they make the T cells and are learning the best ways to use them. Several CAR T-cell therapies are now FDA approved to treat certain kinds of advanced or recurrent lymphomas, and many others are now being studied in clinical trials.

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