



Non-Hodgkin Lymphoma

What is cancer?

The body is made up of trillions of living cells. Normal body cells grow, divide into new cells, and die in an orderly way. During the early years of a person's life, normal cells divide faster to allow the person to grow. Once the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells.

Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. In most cases the cancer cells form a tumor. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell.

Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesn't die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first abnormal cell does.

People can inherit damaged DNA, but most often the DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking. But often no clear cause is found.

Lymphoma doesn't always form tumors. Instead, the cancer cells can involve the blood-forming organs and lymph tissue (discussed in the next section).

Cancer cells often travel to other parts of the body, where they begin to grow and form new tumors that replace normal tissue. This process is called *metastasis*. It happens when the cancer cells get into the bloodstream or lymph vessels of our body.

No matter where a cancer may spread, it is always named (and treated) based on the place it started. For example, breast cancer that has spread to the liver is still called breast cancer, not liver cancer. Likewise, prostate cancer that has spread to the bone is still prostate cancer, not bone cancer.

Different types of cancer can behave very differently. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer.

Not all tumors are cancerous. Tumors that aren't cancer are called *benign*. Benign tumors can cause problems – they can grow very large and press on healthy organs and tissues. But they can't grow into (invade) other tissues. Because they can't invade, they also can't spread to other parts of the body (metastasize). These tumors are almost never life threatening.

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 cells called *lymphocytes*, which are part of the body's immune system. Lymphocytes are in the lymph nodes and other lymphoid tissues (such as the spleen and bone marrow). These will be described in more detail further on.

Some other types of cancer – lung or colon cancers, for example – can spread to lymph tissue such as the lymph nodes. But cancers that start in these places and then spread to the lymph tissue are not lymphomas.

The main types of lymphomas are:

- Hodgkin lymphoma (also known as Hodgkin's lymphoma, Hodgkin disease, or Hodgkin's disease), which is named after Dr. Thomas Hodgkin, who first described it
- Non-Hodgkin lymphoma

These different types of lymphomas behave, spread, and respond to treatment differently.

Doctors can usually tell the difference between them by looking at the cancer cells under a microscope. In some cases, sensitive lab tests may be needed to tell them apart.

Hodgkin disease is discussed in a separate American Cancer Society document. We also have other documents that focus on non-Hodgkin lymphoma in children and lymphoma of the skin.

The rest of this document focuses only on non-Hodgkin lymphoma in adults.

The lymph system and lymphoid tissue

To know what lymphoma is, it helps to understand the body's lymph system.

The lymph system (also known as the *lymphatic system*) is composed mainly of lymphoid tissue, lymph vessels, and a clear fluid called *lymph*. Lymphoid tissue includes the lymph nodes and related organs that are part of the body's immune and blood-forming systems, such as the spleen and bone marrow.

Lymphocytes

Lymphoid tissue is made up of several types of immune system cells that help the body fight infections. Most of the cells in lymphoid tissue are lymphocytes, a type of white blood cell. The main types of lymphocytes are *B lymphocytes* (B cells) and *T lymphocytes* (T cells). Normal B cells and T cells do different jobs within the immune system.

B lymphocytes: 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 immune system cells. Antibodies also attract certain blood proteins that can kill bacteria.

T lymphocytes: There are several types of T cells, each with a special job. Some T cells can directly destroy cells infected with viruses, fungi, or certain kinds of bacteria. T cells can also release substances that attract other types of white blood cells, which then digest the infected cells. Some types of T cells play a role in either boosting or slowing the activity of other immune system cells.

Both types of lymphocytes can develop into lymphoma cells, but B-cell lymphomas are much more common in the United States than T-cell lymphomas. Different types of lymphoma can develop from each type of lymphocyte, based on how mature the cells are when they become cancerous and other factors.

Treatment for each lymphoma depends on which type it is, so determining the exact type of lymphoma is important.

Organs that have lymphoid tissue

Lymphoid tissue is found in many places throughout the body. Because lymphoid tissue is in many parts of the body, lymphomas can start almost anywhere. The major sites of lymphoid tissue are:

Lymph nodes: Lymph nodes are bean-sized organs found throughout the body, including inside the chest, abdomen, and pelvis. They can sometimes be felt under the skin in the neck, under the arms, and in the groin. Lymph nodes are made up mainly of lymphocytes.

The lymph nodes are connected by a system of lymph vessels. These vessels are like veins, except that instead of carrying blood, they carry lymph and lymphocytes.

Lymph nodes get bigger when they fight infection. Lymph nodes that grow in reaction to infection are called *reactive nodes* or *hyperplastic nodes* and are often tender to the touch. An enlarged lymph node is not always a sign of a serious problem. People with sore throats or colds often feel enlarged lymph nodes in the neck. But a large lymph node

is also the most common sign of lymphoma. Lymph node enlargement is discussed more in the section “How is non-Hodgkin lymphoma diagnosed?”

Spleen: The spleen is an organ under the lower part of the rib cage on the left side of the body. An average adult spleen weighs about 5 ounces. The spleen makes lymphocytes and other immune system cells to help fight infection. It also stores healthy blood cells and filters out damaged blood cells, bacteria, and cell waste.

Thymus: The thymus is a small organ behind the upper part of the breastbone and in front of the heart. Before birth, the thymus plays a vital role in development of T lymphocytes. The thymus shrinks and becomes less important over the first 20 years of life. Despite this, it continues to play a role in immune system function.

Adenoids and tonsils: These are collections of lymphoid tissue at the back of the throat. They help make antibodies against germs that are breathed in or swallowed. They are easy to see when they become enlarged during an infection or if they become cancerous.

Digestive tract: The stomach and intestines as well as many other organs also have lymphoid tissue.

Bone marrow: The bone marrow (the soft inner part of certain bones) makes red blood cells, blood platelets, and white blood cells. Red blood cells carry oxygen from the lungs to the rest of the body. Platelets plug up small holes in blood vessels caused by cuts or scrapes. White blood cells’ main job is fighting infections. The main types of white blood cells are granulocytes and lymphocytes. Bone marrow lymphocytes are primarily B cells. Lymphomas sometimes start from bone marrow lymphocytes.

Types of non-Hodgkin lymphoma

Classifying non-Hodgkin lymphoma (NHL) can be quite confusing (even for doctors) because there are so many types and because several different systems have been used. The most recent system is the *World Health Organization (WHO)* classification. The WHO system groups lymphomas based on how they look under a microscope, the chromosome features of the lymphoma cells, and the presence of certain proteins on the surface of the cells. (Older systems classified lymphomas only by how the cells looked under a microscope.)

The more common types of lymphoma are listed below according to whether they are B-cell or T-cell lymphomas. Some rarer forms of non-Hodgkin lymphoma are not discussed here.

B-cell lymphomas

B-cell lymphomas make up most (about 85%) of non-Hodgkin lymphomas in the United States.

Diffuse large B-cell lymphoma

This is the most common type of non-Hodgkin lymphoma in the United States, (about 1 out of every 3 cases). The cells look fairly large when seen with a microscope.

Diffuse large B-cell lymphoma (DLBCL) can affect any age group but occurs mostly in older people (the average age is mid-60s). It usually starts as a quickly growing mass in a lymph node deep inside the body, such as in the chest or abdomen, or in a lymph node you can feel, such as in the neck or armpit. It can also start in other areas such as the intestines, bone, or even the brain or spinal cord.

About 1 in 3 of these lymphomas is only in one part of the body (localized) when it is found. Lymphomas are easier to treat when they are localized than when they have spread to other parts of the body.

Genetic tests have shown that there are different subtypes of DLBCL, even though they look the same under the microscope. These subtypes seem to have different outcomes (prognoses) and responses to treatment.

DLBCL is a fast-growing lymphoma, but it often responds well to treatment. Overall, about 3 out of 4 people will have no signs of disease after the initial treatment, and many are cured with therapy.

Primary mediastinal B-cell lymphoma: This is a subtype of DLBCL in which the lymphoma cells are large but there is a lot of fibrosis (scar-like tissue) in the background. It accounts for about 2% of all lymphomas. About 2 out of 3 people with this lymphoma are women. Most are young – in their 30s.

This lymphoma starts in the mediastinum (the area in the middle of the chest behind the breastbone). It is usually localized when it is found. It can cause trouble breathing because it often presses on the windpipe (trachea) leading into the lungs. It can also block the superior vena cava (the large vein that returns blood to the heart from the arms and head), which can make the arms and face swell.

This is a fast-growing lymphoma, but it usually responds well to treatment.

Intravascular large B-cell lymphoma: In this rare subtype of DLBCL, the lymphoma cells are only found inside blood vessels, not in the lymph nodes or bone marrow. It is treated like DLBCL.

Follicular lymphoma

About 1 out of 5 lymphomas in the United States is follicular lymphoma. The term follicular means that the cells tend to grow in a circular pattern in lymph nodes.

The average age for people with this lymphoma is about 60. It's rare in very young people. Most of the time, this lymphoma occurs in many lymph node sites in the body, as well as in the bone marrow.

Follicular lymphomas are often slow-growing and respond well to treatment, but they are hard to cure. These lymphomas may not require treatment when they are first diagnosed. Instead, treatment may be delayed until the lymphoma is causing problems. Over time, about 1 in 3 follicular lymphomas turns into a fast-growing diffuse B-cell lymphoma.

Chronic lymphocytic leukemia /small lymphocytic lymphoma

These 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 chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (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. About 5% to 10% of all lymphomas are SLLs.

Both CLL and SLL are slow-growing diseases, although CLL, which is much more common, tends to grow more slowly. Treatment is the same for CLL and SLL. They are usually not curable with standard treatments, but depending on the stage and growth rate of the disease, most patients live longer than 10 years. Sometimes, these slow-growing lymphomas turn into a more aggressive type.

For more detailed information, see our document *Leukemia -- Chronic Lymphocytic*.

Mantle cell lymphoma

Only about 5% of lymphomas are this type. The cell size is small to medium.

Men are affected most often. The average age of patients is the early 60s. When this lymphoma is diagnosed, it is usually widespread in the lymph nodes, bone marrow, and often the spleen.

This usually isn't a very fast-growing lymphoma, but it can be challenging to treat. Newer treatments might be more effective than those used in the past, and may offer a better chance for long-term survival for patients now being diagnosed.

Marginal zone B-cell lymphomas

Marginal zone lymphomas account for about 5% to 10% of lymphomas. The cells in these lymphomas look small under the microscope. There are 3 main types of marginal zone lymphomas.

Extranodal marginal zone B-cell lymphomas, also known as mucosa-associated lymphoid tissue (MALT) lymphomas: These lymphomas start in places other than the lymph nodes (extranodal) and are the most common type. Most MALT lymphomas start in the stomach and are linked to infection by *Helicobacter pylori*, which is the bacteria that causes many stomach ulcers. Other possible sites of MALT lymphomas include the lung, skin, thyroid, salivary glands, and tissues surrounding the eye. Usually it is confined to the area where it begins and is not widespread. Many of these other MALT lymphomas have also been linked to infections with bacteria or viruses.

The average age of patients with MALT lymphoma is about 60. It is a slow-growing lymphoma and is often curable in its early stages. Doctors often use antibiotics as the first treatment for MALT lymphoma of the stomach, because treating the *Helicobacter pylori* infection often cures the lymphoma.

Nodal marginal zone B-cell lymphoma: This is a rare disease, found mainly in older women. It usually stays in the lymph nodes, although lymphoma cells can also sometimes be found in the bone marrow.

This lymphoma tends to be slow-growing (although not usually as slow as MALT lymphoma), and many patients are cured if they are diagnosed when the disease is in the early stages.

Splenic marginal zone B-cell lymphoma: This is a rare lymphoma. Most often the lymphoma is found only in the spleen and bone marrow.

Patients are often elderly and male and have fatigue and discomfort caused by an enlarged spleen. Because the disease is slow-growing, they might not need treatment unless the symptoms become troublesome. This type of lymphoma has been linked to infection with the hepatitis C virus.

Burkitt lymphoma

This type makes up about 1% to 2% of all lymphomas. It is named after the doctor who first described this disease in African children and young adults. The cells are medium-sized. Another kind of lymphoma, Burkitt-like lymphoma, has slightly larger cells. Because this second kind of lymphoma is hard to tell apart from Burkitt lymphoma, the WHO classification combines them.

This is a very fast-growing lymphoma. In the African (or *endemic*) variety, it often starts as a tumor of the jaw or other facial bones. It is linked to infection with the Epstein-Barr virus (which can also cause infectious mononucleosis or “mono”). The endemic type of Burkitt lymphoma is rare in the United States.

In the types seen more often in the United States, the lymphoma usually starts in the abdomen, where it forms a large tumor mass. It can also start in the ovaries, testicles, or other organs, and can spread to the brain and spinal fluid. The type seen in the United States is usually not linked to Epstein-Barr viral infection.

Close to 90% of patients are male, and the average age in the US is about 30. Although this is a fast-growing lymphoma, more than half of patients can be cured by intensive chemotherapy.

Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)

This type is not common, accounting for only 1% to 2% of lymphomas. The lymphoma cells are small and found mainly in the bone marrow, lymph nodes, and spleen. It is discussed in detail in our document *Waldenstrom Macroglobulinemia*.

Hairy cell leukemia

Despite the name, this is sometimes considered to be a type of lymphoma. Hairy cell leukemia (HCL) is rare – about 700 people in the United States are diagnosed with it each year. The cells are small B lymphocytes with projections coming off them that give them a “hairy” appearance. They are typically found in the bone marrow and spleen and in the blood.

Men are more likely to get HCL than women, and the average age is around 50.

Hairy cell leukemia is slow-growing, and some patients may never need treatment. An enlarging spleen or dropping blood cell counts (due to cancer cells invading the bone marrow) are the usual reasons to begin treatment. If treatment is needed, it’s usually very effective.

Hairy cell leukemia is also described in our document *Leukemia--Chronic Lymphocytic*

Primary central nervous system (CNS) lymphoma

This lymphoma usually involves the brain (called *primary brain lymphoma*), but it may also be found in the spinal cord and in tissues around the spinal cord and the eye. Over time, it tends to become widespread in the central nervous system.

Primary CNS lymphoma is rare overall, but it’s more common in people with immune system problems, such as those infected with HIV, the virus that causes AIDS. Most people develop headaches and confusion. They can also have vision problems; weakness or altered sensation in the face, arms, or legs; and in some cases, seizures.

The outlook for people with this condition has always been thought to be fairly poor, but some people can live at least 5 years with today’s treatments.

Lymphoma of the eye (primary intraocular lymphoma), which is related to primary CNS lymphoma, is discussed in our document *Eye Cancer (Melanoma and Lymphoma)*.

T-cell lymphomas

T-cell lymphomas make up less than 15% of non-Hodgkin lymphomas in the United States. There are many types of T-cell lymphoma, but they are all fairly rare.

Precursor T-lymphoblastic lymphoma/leukemia

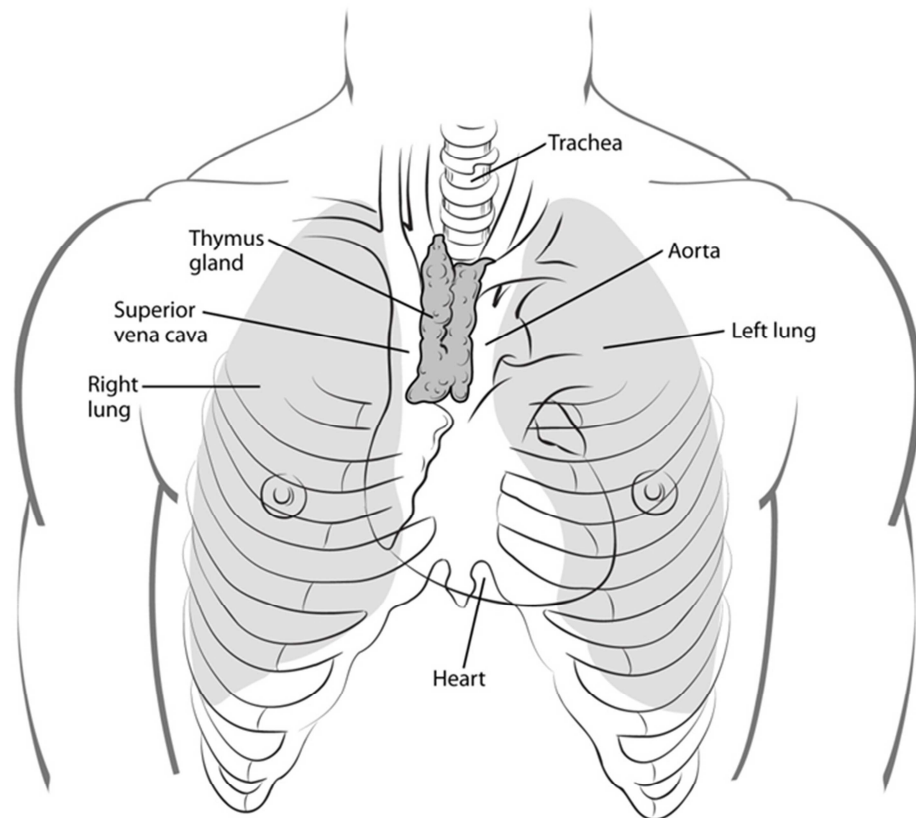
This disease accounts for about 1% of all lymphomas. It can be considered either a lymphoma or leukemia, depending on how much of the bone marrow is involved (leukemias have more bone marrow involvement). The cancer cells are small-to-medium sized, immature T-cells.

This lymphoma often starts in the thymus (see the image below). This is where many T cells are made. This lymphoma can develop into a large tumor in the mediastinum (the

area in the middle of the chest and behind the breast bone). If the tumor presses on the windpipe (trachea) that carries air into the lungs, it can cause trouble breathing. The tumor can also press on or even block the superior vena cava (the large vein that returns blood to the heart from the arms and head), which can make the arms and face swell.

Patients are most often young adults, with males being affected more often than females.

This lymphoma is fast-growing, but if it hasn't spread to the bone marrow when it is first diagnosed, the chance of cure with chemotherapy is quite good.



Often, the lymphoma form of this disease is treated in the same way as the leukemia form. For more information, see our document *Leukemia - Acute Lymphocytic (Adults)*.

Peripheral T-cell lymphomas

These types of lymphomas develop from more mature forms of T cells. They are rare, accounting for only a small portion of all lymphomas.

Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome, and others):

These lymphomas start in the skin. Skin lymphomas account for about 5% of all lymphomas. They are described in our document *Lymphoma of the Skin*.

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 the HTLV-1 virus is more common. There are 4 subtypes: smoldering, chronic, acute, and lymphoma.

The **smoldering** subtype has abnormal T-cells in the blood without an increased number of lymphocytes in the blood. This lymphoma may involve the skin or lungs, but there is no involvement of other tissues. The smoldering type grows slowly and has a good prognosis.

The **chronic** subtype also grows slowly and has a good prognosis. It has an increase in total lymphocytes and T-cells in the blood. It may involve the skin, lungs, lymph nodes, liver, and/or spleen, but not other tissues.

The **acute** subtype acts like acute leukemia. It has high lymphocyte and T-cell counts, often along with enlargement of lymph nodes, liver, and spleen. The skin and other organs may be involved with lymphoma as well. Patients often have fever, night sweats, and/or weight loss, as well as certain abnormal blood test results.

The **lymphoma** subtype grows more quickly than the chronic and smoldering types, but not as fast as the acute type. It has enlarged lymph nodes without increased lymphocytes in the blood, and the T-cell count is not high.

Angioimmunoblastic T-cell lymphoma: This lymphoma accounts for about 3% of all lymphomas. It is more common in older adults. It tends to involve the lymph nodes as well as the spleen or liver, which can cause them to be enlarged. Patients usually have fever, weight loss, and skin rashes and often develop infections. This lymphoma often progresses quickly. Treatment is often effective at first, but the lymphoma tends to come back (recur).

Extranodal natural killer/T-cell lymphoma, nasal type: This rare type often involves the upper airway passages, such as the nose and upper throat, but it can also invade the skin and digestive tract. It is much more common in parts of Asia and South America. Cells of this lymphoma are similar in some ways to normal natural killer (NK) cells. NK cells are lymphocytes that can respond to infections more quickly than T-cells and B-cells.

Enteropathy-associated intestinal T-cell lymphoma (EATL): EATL is a lymphoma that occurs in the lining of the intestine. This lymphoma is most common in the jejunum (the second part of the small intestine), but can also occur elsewhere in the small intestine and in the colon. EATL often affects more than one place in the intestine, and may spread to the nearby lymph nodes, as well. It can cause the intestine to become blocked (*obstruction*) or a hole to develop in the intestine (a *perforation*). If either of these occur, the symptoms can include severe abdominal (belly) pain, nausea, and vomiting. There are 2 subtypes of this lymphoma.

- **Type I EATL** occurs in people with a disease called *gluten-sensitive enteropathy* (also known as *celiac disease*, *celiac sprue*, or *sprue*). Sprue is an autoimmune disease in which gluten, the main protein in wheat flour, causes the body produce antibodies that attack the lining of the intestine and other parts of the body. Type I EATL is rare among people who have had sprue since childhood, and is more often seen in people diagnosed as adults who have had sprue for a long time. It is most common in people with sprue that hasn't been well controlled on a gluten free diet. Still, type I EATL can sometimes occur in people who didn't realize that they had sprue before the lymphoma was found. This lymphoma is more common in men than women, and tends to occur in people in their 60s and 70s. People who do not tolerate gluten, but don't have sprue, do not seem to have an increased risk of this type of lymphoma.
- **Type II EATL** is not linked to sprue and looks different than type I under the microscope. Type II EATL is less common than type I.

Anaplastic large cell lymphoma (ALCL): About 2% of lymphomas are of this type. It is more common in young people (including children), but it does occur in people in their 50s and 60s. It usually starts in lymph nodes and can also spread to skin. This type of lymphoma tends to be fast-growing, but many people with this lymphoma are cured with aggressive chemotherapy.

The main forms of ALCL are **primary cutaneous**, which only affects the skin, and **systemic**. Systemic ALCL is divided into 2 types based on whether a gene change is present in the lymphoma cells that causes them to make a lot of protein called *anaplastic lymphoma kinase* or *ALK1*. ALK-positive ALCL tends to occur in younger patients and tends to have a better prognosis (outlook) than the ALK-negative type.

Primary cutaneous ALCL isn't discussed further in this document, but is described in our document *Lymphoma of the Skin*.

Peripheral T-cell lymphoma, unspecified: This name is given to T-cell lymphomas that don't readily fit into any of the groups above. They make up about half of all T-cell lymphomas. The tumor cells can be small or large. Most people diagnosed with this disease are in their 60s. This lymphoma often involves lymph nodes, but it can affect the skin, bone marrow, liver, and GI (gastrointestinal) tract, as well. As a group, these lymphomas tend to be widespread and grow quickly. Some patients respond well to chemotherapy, but long-term survival is not common.

What are the key statistics about 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 most recent estimates for non-Hodgkin's lymphoma for 2015 are:

- About 71,850 people (39,850 males and 32,000 females) will be diagnosed with NHL. This includes both adults and children.
- About 19,790 people will die from this cancer (11,480 males and 8,310 females).

The average American's risk of developing NHL during his or her lifetime is about 1 in 50. Each person's risk may be affected by certain risk factors (listed in the next section).

Death rates from NHL have been decreasing since the late 1990s.

Although some types of NHL are among the more common childhood cancers, more than 95% of cases occur in adults. The types of NHL seen in children are often very different from those seen in adults. For more information, see our document *Non-Hodgkin Lymphoma in Children*.

NHL can occur at any age, but about half of patients are older than 66. The risk of developing NHL increases throughout life. The aging of the American population is likely to lead to an increase in NHL cases during the coming years.

What are the risk factors for non-Hodgkin lymphoma?

A risk factor is something that affects your chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, like smoking, can be changed; others, like a person's age or family history, can't.

But risk factors don't tell us everything. Having a risk factor, or even many risk factors, does not mean that you will get the disease. And many people who get the disease may have few or no known risk factors. Even if a person with non-Hodgkin lymphoma has a risk factor, it's often very hard to know how much that risk factor may have contributed that person developing lymphoma.

Researchers have found several factors that may affect a person's chance of getting non-Hodgkin lymphoma. There are many types of lymphoma, and some of these factors have been linked only to certain types.

Age

Getting older is a strong risk factor for lymphoma overall, with most cases occurring in people in their 60s or older. But some types of lymphoma are more common in younger people.

Gender

Overall, the risk of non-Hodgkin lymphoma is higher in men than in women, but there are certain types of non-Hodgkin lymphoma that are more common in women. The reasons for this are not known.

Race, ethnicity, and geography

In the United States, whites are more likely than African Americans and Asian Americans to develop non-Hodgkin lymphoma.

Worldwide, non-Hodgkin lymphoma is more common in developed countries, with the United States and Europe having the highest rates. Some types of lymphoma that have been linked to specific infections (described further on) are more common in certain parts of the world.

Exposure to certain chemicals

Some studies have suggested that chemicals such as benzene and certain herbicides and insecticides (weed- and insect-killing substances) may be linked with an increased risk of non-Hodgkin lymphoma. Research to clarify these possible links is still in progress.

Some chemotherapy drugs used to treat other cancers may increase the risk of developing non-Hodgkin lymphoma many years later. For example, patients who have been treated for Hodgkin disease have an increased risk of later developing non-Hodgkin lymphoma. But it's not totally clear if this is related to the disease itself or if it is an effect of the treatment.

Radiation exposure

Studies of survivors of atomic bombs and nuclear reactor accidents have shown they have an increased risk of developing several types of cancer, including leukemia, thyroid cancer, and non-Hodgkin lymphoma.

Patients treated with radiation therapy for some other cancers, such as Hodgkin disease, have a slightly increased risk of developing non-Hodgkin lymphoma later in life. This risk is greater for patients treated with both radiation therapy and chemotherapy.

Immune system deficiency

People with weakened immune systems have an increased risk for non-Hodgkin lymphoma. For example, people who receive organ transplants (kidney, heart, liver) are treated with drugs that suppress their immune system to prevent it from attacking the new organ. These people have a higher risk of developing non-Hodgkin lymphoma.

The human immunodeficiency virus (HIV) can also weaken the immune system, and people infected with HIV are at increased risk of non-Hodgkin lymphoma.

Some genetic (inherited) syndromes can cause children to be born with a deficient immune system. Along with an increased risk of serious infections, these children also have a higher risk of developing non-Hodgkin lymphoma. These inherited immune deficiency diseases can be passed on to children, but people with non-Hodgkin

lymphoma who don't have these inherited diseases do not pass an increased risk of lymphoma on to their children.

Autoimmune diseases

Some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE or lupus), Sjogren (Sjögren) disease, celiac sprue (gluten-sensitive enteropathy), and others have been linked with an increased rate of non-Hodgkin lymphoma.

In autoimmune diseases, the immune system sees the body's own tissues as foreign and attacks them, as it would a germ. Lymphocytes (the cells from which lymphomas start) are part of the body's immune system. The overactive immune system in autoimmune diseases may make lymphocytes grow and divide more often than normal. This might increase the risk of them developing into lymphoma cells.

Certain infections

Some types of infections may raise the risk of non-Hodgkin lymphoma in different ways.

Infections that directly transform lymphocytes

Some viruses can directly affect the DNA of lymphocytes, helping to transform them into cancer cells. The human T-cell leukemia/lymphoma virus (HTLV-1) and the Epstein-Barr virus (EBV) seem to work in this way.

Infection with HTLV-1 increases a person's risk of developing certain types of T-cell lymphoma. This virus is most common in some parts of Japan and in the Caribbean region, but is found throughout the world. In the United States, it causes less than 1% of lymphomas. HTLV-1 spreads through sex and contaminated blood and can be passed to children through breast milk from an infected mother.

Infection with the Epstein-Barr virus (EBV) is an important risk factor for Burkitt lymphoma in areas of Africa where this type of lymphoma is common. In developed countries such as the United States, EBV is more often linked with lymphomas in patients also infected with HIV, the virus that causes AIDS. It has also been linked with developing nasal-type extranodal natural killer/ T-cell lymphoma, lymphomatoid granulomatosis (a form of B-cell lymphoma), and post-transplant lymphoproliferative disorder.

Human herpes virus 8 (HHV8) can also infect lymphocytes, leading to a rare type of lymphoma called *primary effusion lymphoma*. This lymphoma is most often seen in patients who are infected with HIV. HHV8 infection is also linked to another cancer, Kaposi sarcoma. For this reason, another name for this virus is *Kaposi sarcoma-associated herpes virus* (KSHV).

Infections that weaken the immune system

Infection with human immunodeficiency virus (HIV), also known as the AIDS virus, commonly causes immune system deficiency. HIV infection is a risk factor for developing certain types of non-Hodgkin lymphoma, such as Burkitt lymphoma and diffuse large B-cell lymphoma.

Infections that cause chronic immune stimulation

Some long-term infections may increase a person's risk of lymphoma by forcing their immune system to be constantly activated. As more lymphocytes are made to fight the infection, there is a greater chance for genetic mistakes to occur, which might eventually lead to lymphoma.

Helicobacter pylori, a type of bacteria known to cause stomach ulcers, has also been linked to mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. The body's immune reaction to this infection increases the risk of lymphoma. This is important because antibiotics can help treat some patients who have MALT lymphomas of the stomach that test positive for *H. pylori*.

Chlamydomphila psittaci (formerly known as *Chlamydia psittaci*) is a bacteria that can infect both humans and animals. In humans, it can cause a lung infection called *psittacosis*. DNA from this bacterium has been found in biopsies of MALT lymphoma in the tissues around the eye (called *ocular adnexal marginal zone lymphoma*). This is a sign of infection. A recent study has shown that treating the infection with an antibiotic (doxycycline) can make this lymphoma get better and even go away.

Infection with the bacterium *Campylobacter jejuni* has been linked to a type of MALT lymphoma called *immunoproliferative small intestinal disease*. This type of lymphoma, which is also sometimes called *Mediterranean abdominal lymphoma*, typically occurs in young adults in eastern Mediterranean countries. Antibiotics can be helpful in treating this lymphoma, especially in early stages.

The hepatitis C virus (HCV) can also cause long-term infections. Infection with HCV seems to be a risk factor for certain types of lymphoma. In splenic marginal zone lymphoma, if the HCV infection is treated successfully, the lymphoma might get better and even go away.

Body weight and diet

Some studies have suggested that being overweight or obese may increase your risk of non-Hodgkin lymphoma. Other studies have suggested that a diet high in fat and meats may raise your risk. More research is needed to confirm these findings. In any event, staying at a healthy weight and eating a healthy diet have many known health benefits outside of the possible effect on lymphoma risk.

Breast implants

Although it is rare, some women develop anaplastic large cell lymphoma in the scar tissue around their breast implants.

Do we know what causes non-Hodgkin lymphoma?

Researchers have found that non-Hodgkin lymphoma is linked with a number of risk factors, but the causes of most lymphomas are unknown. This is complicated by the fact that lymphomas are actually a diverse group of cancers.

Still, scientists have made a lot of progress in understanding how certain changes in DNA can cause normal lymphocytes to become lymphoma cells. Normal human cells grow and function mainly based on the information contained in each cell's chromosomes. Human DNA is packaged in 23 pairs of chromosomes, which are long molecules of DNA in each cell. DNA is the chemical that makes up our genes – the instructions for how our cells function. We look like our parents because they are the source of our DNA. But DNA affects more than how we look.

Some genes control when cells grow and divide. Genes that speed up cell division or help cells live longer are called *oncogenes*. Others that slow down cell division or make cells die at the right time are called *tumor suppressor genes*.

Each time a cell prepares to divide into 2 new cells, it must make a new copy of the DNA in its chromosomes. This process is not perfect, and errors can occur that may affect genes within the DNA. Cancers can be caused by DNA mutations (changes) that turn on oncogenes or turn off tumor suppressor genes.

Some people inherit DNA mutations from a parent that increase their risk for some types of cancer. But non-Hodgkin lymphoma is not one of the cancer types often caused by these inherited mutations. In other words, there's no increased risk of lymphoma in the children of patients with lymphoma.

DNA changes related to non-Hodgkin lymphoma are usually acquired after birth, rather than being inherited. Acquired changes may result from exposure to radiation, cancer-causing chemicals, or infections, but often these changes occur for no apparent reason. They seem to happen more often as we age, and lymphomas for the most part are a cancer of older people.

Translocations are a type of DNA change that can cause non-Hodgkin lymphoma to develop. A translocation means that DNA from one chromosome breaks off and becomes attached to a different chromosome. When this happens, oncogenes can be turned on or tumor suppressor genes can be turned off. Some lymphomas tend to have specific chromosome defects. For example, most cases of follicular lymphoma have a translocation between chromosomes 14 and 18, which turns on the *bcl-2* oncogene. This stops the cell from dying at the right time, which can lead to lymphoma.

Scientists are learning much about the exact gene changes involved in lymphoma. This information is being used to develop more accurate tests to detect and classify certain types of lymphoma. Hopefully, these discoveries can be used to develop new treatments as well.

Researchers are beginning to understand how these gene changes develop in people with certain risk factors, but they still do not know why most lymphomas develop in people with no apparent risk factors.

Lymphocytes (the cells from which lymphomas start) are immune system cells, so it's not surprising that changes in the immune system seem to play an important role in many cases of lymphoma.

- People with immune deficiencies (due to inherited conditions, drug treatment, organ transplants, or HIV infection) have a much higher chance of developing lymphoma than people without an immune deficiency.
- People with certain autoimmune diseases (where the immune system constantly attacks a certain part of the body) have an increased risk of getting lymphoma.
- People with certain chronic infections are also at increased risk, probably because the immune system is constantly making new lymphocytes to fight the infection, which increases the chances for mistakes in their DNA.

Can non-Hodgkin lymphoma be prevented?

Most people with non-Hodgkin lymphoma have no risk factors that can be changed, so there is no way to protect against these lymphomas. For now, the best way to reduce the risk for non-Hodgkin lymphoma is to try to prevent known risk factors such as immune deficiency.

Infection with the human immunodeficiency virus (HIV) is a preventable cause of immune deficiency. HIV is spread among adults mostly through unprotected sex and by injection drug users sharing contaminated needles. Blood transfusions are now an extremely rare source of HIV infection. Curbing the spread of HIV would prevent many deaths from non-Hodgkin lymphoma. Treating HIV with anti-HIV drugs also lowers the chance of developing non-Hodgkin lymphoma.

Preventing the spread of the human T-cell leukemia/lymphoma virus (HTLV-1) could have a great impact on non-Hodgkin lymphoma in areas of the world where this virus is common, such as Japan and the Caribbean region. The virus is rare in the United States but seems to be increasing in some areas. The same strategies used to prevent HIV spread could also help control HTLV-1.

Helicobacter pylori infection has been linked to some lymphomas of the stomach. Treating *H. pylori* infections with antibiotics and antacids may lower this risk, but the benefit of this strategy has not been proven yet. Most people with *H. pylori* infection

have no symptoms, and some have only mild heartburn. More research is needed to find the best way to detect and treat this infection in people without symptoms.

Another risk factor for non-Hodgkin lymphoma is infection with the Epstein-Barr virus (the cause of infectious mononucleosis, or mono), but there is no known way of preventing this infection.

Some lymphomas are caused by treatment of cancers with radiation and chemotherapy or by the use of immune-suppressing drugs to avoid rejection of transplanted organs. Doctors are trying to find better ways to treat cancer and organ transplant patients without increasing the risk of lymphoma as much. But for now, the benefits of these treatments still usually outweigh the small risk of developing lymphoma many years later.

Some studies have suggested that being overweight or obese may increase your risk of non-Hodgkin lymphoma. Other studies have suggested that a diet high in fat and meats may raise your risk. Staying at a healthy weight and eating a healthy diet may help protect against lymphoma, but more research is needed to confirm this.

Can non-Hodgkin lymphoma be found early?

At this time, there are no widely recommended screening tests for this cancer. (Screening is testing for cancer in people without any symptoms.) Still, in some cases lymphoma can be found early.

The best way to find this cancer early is prompt attention to the signs and symptoms of this disease, which are discussed in the section “How is non-Hodgkin lymphoma diagnosed?”

Careful, regular medical check-ups are important for people with known risk factors for non-Hodgkin lymphoma (such as HIV infections, organ transplants, autoimmune disease, or prior cancer treatment). These people do not commonly develop lymphoma, but they and their doctors should be aware of possible symptoms and signs of lymphoma.

Signs and symptoms of non-Hodgkin lymphoma

Non-Hodgkin lymphoma can cause many different signs and symptoms, depending on where it is in the body. In some cases it might not cause any symptoms until it grows quite large. Common signs and symptoms include:

- Enlarged lymph nodes
- Swollen abdomen (belly)
- Feeling full after only a small amount of food
- Chest pain or pressure

- Shortness of breath or cough
- Fever
- Weight loss
- Night sweats
- Fatigue (extreme tiredness)
- Low red blood cell counts (anemia)

Swollen lymph nodes

Non-Hodgkin lymphoma can cause lymph nodes to become enlarged. When this occurs in lymph nodes close to the surface of the body (such as on the sides of the neck, in the groin or underarm areas, or above the collar bone), they may be seen or felt as lumps under the skin. These are often found by the patient, a family member, or a health care professional. Although enlarged lymph nodes are a common symptom of lymphoma, they are much more often caused by infections.

Lymphoma in the abdomen

Lymphomas in the abdomen can cause it to become swollen and tender. This could be because of lymph nodes in the abdomen enlarging, but it can also be caused by the build-up of large amounts of fluid.

Lymphoma can enlarge the spleen so that it presses on the stomach. This can make a person feel full after eating only a small amount of food.

When lymphoma is in the intestines or causes swelling near the intestines, bowel movements may be blocked, which may lead to abdominal pain, nausea, or vomiting. Lymphoma in the intestines can also cause holes to develop in the intestine wall (called *perforations*). This allows the contents of the intestines to leak out into the abdominal cavity, leading to serious infection and severe pain with nausea and vomiting.

Lymphomas of the stomach often cause stomach pain, nausea, and reduced appetite.

Lymphoma in the chest

When lymphoma starts in the thymus or lymph nodes in the chest, it may press on the nearby trachea (windpipe), which can cause coughing or trouble breathing. Lymphomas in this area can also cause a feeling of chest pain or pressure.

The superior vena cava (SVC) is the large vein that carries blood from the head and arms back to the heart. It passes near the thymus and lymph nodes inside the chest. Lymphomas in this area may push on the SVC, which can cause the blood to back up in the veins. This can lead to swelling (and sometimes a bluish-red color) in the head, arms, and upper chest. It can also cause trouble breathing and a change in consciousness if it

affects the brain. This condition, known as *SVC syndrome*, can be life-threatening and must be treated right away.

Lymphoma affecting the brain

Lymphomas of the brain, called *primary brain lymphomas*, can cause headache, trouble thinking, weakness in parts of the body, personality changes, and sometimes seizures.

Other types of lymphoma can spread to the area around the brain and spinal cord. This can cause problems such as double vision, facial numbness, and trouble speaking.

Lymphoma in the skin

Lymphomas of the skin may be seen or felt. They often appear as extremely itchy, red or purple lumps or nodules under the skin. (For more details, see our document *Lymphoma of the Skin*.)

General symptoms

B symptoms

Along with causing symptoms and signs in the part of the body where it starts, non-Hodgkin lymphoma can also cause general symptoms, such as:

- Unexplained weight loss
- Fever
- Drenching night sweats (enough to soak clothing and sheets)

When talking about lymphoma, doctors call these *B symptoms*. B symptoms are most common in more rapidly growing lymphomas. These symptoms are important not only in helping diagnose non-Hodgkin lymphoma, but also in determining the stage and prognosis (outlook) if lymphoma is found (see “How is non-Hodgkin lymphoma staged?”).

Symptoms caused by low blood cell counts

If lymphoma cells are in the bone marrow they can crowd out the normal, healthy cells that make new blood cells. This can lead to problems like:

- Severe or frequent infections (from low white blood cell counts)
- Easy bruising or bleeding (from low blood platelet counts)
- Fatigue (from low red blood cell counts: anemia)

Anemia can also occur if the lymphoma cells cause the body to destroy red blood cells (this is called *hemolytic anemia*).

Many symptoms of lymphoma can be caused by things other than cancer. Still, if you are having symptoms, you should see your doctor so the cause can be found.

How is non-Hodgkin lymphoma diagnosed?

Most people with non-Hodgkin lymphoma (NHL) see their doctor because they have felt a lump that hasn't gone away, they develop some of the other symptoms of NHL (see the previous section), or they just don't feel well and go in for a check-up.

If signs or symptoms suggest that a person might have non-Hodgkin lymphoma, exams and tests will be done to find out for certain if they do and, if so, to determine the exact type of lymphoma.

Medical history and physical exam

If your symptoms suggest you might have non-Hodgkin lymphoma, your doctor will want to get a thorough medical history, including information about your symptoms, possible risk factors, family history, and other medical conditions.

Next, the doctor will examine you, paying special attention to the lymph nodes and other areas of the body that might be involved, including the spleen and liver. Because infections are the most common cause of enlarged lymph nodes, the doctor will look for an infection in the part of the body near the swollen lymph nodes.

If the doctor suspects that non-Hodgkin lymphoma might be causing the symptoms, he or she will recommend a biopsy of the area.

Biopsy

Many symptoms of non-Hodgkin lymphoma are not specific enough to say for certain if they are being caused by cancer. Most of them can also be caused by non-cancerous problems, like infections, or by other kinds of cancers.

For example, enlarged lymph nodes are more often caused by infections than by non-Hodgkin lymphoma. Because of this, doctors often prescribe antibiotics and wait a few weeks to see if the nodes shrink.

If the nodes stay the same or continue to grow, the doctor might then order a biopsy. Either a small piece of a node or, more commonly, the entire node is removed for viewing under the microscope and for other lab tests.

A biopsy might be needed right away if the size, texture, or location of the node or the presence of other symptoms strongly suggests cancer. But delaying the diagnosis for a few weeks is not likely to be harmful unless it's a very fast-growing lymphoma.

Types of biopsies used to diagnose non-Hodgkin lymphoma

A biopsy is the only way to diagnose non-Hodgkin lymphoma. There are several types of biopsies. Doctors choose which one to use based on each person's situation.

Excisional or incisional biopsy: This is the most common type of biopsy if lymphoma is suspected. In this procedure, a surgeon cuts through the skin to remove either the entire node (excisional biopsy) or a small part of a large tumor (incisional biopsy).

If the enlarged node is near the skin surface, this is a simple operation that can often be done with local anesthesia (numbing medicine). But if it is inside the chest or abdomen, the patient will be sedated or given general anesthesia (drugs are used to put the patient into a deep sleep).

This method almost always provides enough of a sample to diagnose the exact type of non-Hodgkin lymphoma. It is the preferred type of biopsy, if it can be done without too much discomfort to the patient.

Fine needle aspiration (FNA) or core needle biopsy: In an FNA biopsy, the doctor uses a very thin, hollow needle attached to a syringe to withdraw (aspirate) a small amount of tissue from an enlarged lymph node or a tumor mass. For a core needle biopsy, the doctor uses a larger needle to remove a slightly larger piece of tissue.

If the enlarged node is near the surface of the body, the doctor can aim the needle while feeling the node. If the tumor is deep inside the body, the doctor can guide the needle using a computed tomography (CT) scan or ultrasound (see descriptions of imaging tests later in this section).

A needle biopsy does not require surgery, but in some cases it might not remove enough of a sample to make a definite diagnosis. Most doctors do not use needle biopsies to diagnose lymphoma. But if the doctor suspects that your lymph node is enlarged because of an infection or by the spread of cancer from another organ (such as the breast, lungs, or thyroid), a needle biopsy may be the first type of biopsy done. An excisional biopsy might still be needed to diagnose and classify lymphoma, even after a needle biopsy has been done.

Once lymphoma has been diagnosed, needle biopsies are sometimes used to check areas in other parts of the body that might be lymphoma spreading or coming back after treatment.

Other types of biopsies

These procedures are not normally done to diagnose lymphoma, but they might be used to help determine the stage (extent) of a lymphoma that has already been diagnosed. They may also be done for symptoms or problems even when lymphoma is not suspected, and lymphoma may be found.

Bone marrow aspiration and biopsy: These procedures are often done after lymphoma has been diagnosed to help determine if it has reached the bone marrow. The 2 tests are often done at the same time. The samples are usually taken from the back of the pelvic (hip) bone, although in some cases they may be taken from the sternum (breast bone) or other bones.

For a bone marrow *aspiration*, you lie on a table (either on your side or on your belly). After cleaning the skin over the hip, the doctor numbs the area and the surface of the bone with local anesthetic, which can cause a brief stinging or burning sensation. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow (about 1 teaspoon). Even with the anesthetic, most patients still have some brief pain when the marrow is removed.

A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow is removed with a slightly larger needle that is twisted as it is pushed into the bone. Most patients feel pressure during the biopsy, but it can cause some brief pain. Once the biopsy is done, pressure will be applied to the site to help stop any bleeding.

Lumbar puncture (spinal tap): This test looks for lymphoma cells in the cerebrospinal fluid (CSF), which is the liquid that bathes the brain and spinal cord.

For this test, the patient may lie on their side or sit up. The doctor first numbs an area in the lower part of the back over the spine. A small, hollow needle is then placed between the bones of the spine to withdraw some of the fluid.

Most people with lymphoma will not need this test. But doctors may order it for certain types of lymphoma or if a person has symptoms that suggest the lymphoma may have reached the brain.

Pleural or peritoneal fluid sampling: Lymphoma that has spread to the chest or abdomen can cause fluid to build up. Pleural fluid (inside the chest) or peritoneal fluid (inside the abdomen) can be removed by placing a hollow needle through the skin into the chest or abdomen. Often, ultrasound is used to guide the needle. The doctor uses a local anesthetic to numb the skin before inserting the needle. The fluid is then withdrawn and looked at under the microscope to check for lymphoma cells. When this procedure is used to remove fluid from the area around the lung, it is called a *thoracentesis*. When it is used to collect fluid from inside the abdomen, it's known as a *paracentesis*.

Lab tests on biopsy samples to diagnose and classify lymphoma

All biopsy samples and fluids are looked at under a microscope by a pathologist (a doctor with special training in recognizing cancer cells), who studies the size and shape of the cells and how they are arranged. This may show not only if the person has a lymphoma, but also what type of lymphoma it is. Because diagnosing lymphoma can be tricky, it helps if the pathologist specializes in diseases of the blood.

Pathologists can sometimes tell which kind of lymphoma a patient has by looking at the cells, but usually other types of tests are needed to confirm the diagnosis.

Immunohistochemistry

In this test, a part of the biopsy sample is treated with special antibodies (man-made versions of immune system proteins) that attach only to specific molecules on the cell

surface. These antibodies cause color changes, which can be seen under a microscope. This test may be helpful in distinguishing different types of lymphoma from one another and from other diseases.

Flow cytometry

Like immunohistochemistry, this test looks for certain substances on the outside surface of cells that help identify what types of cells they are. But this test can look at many more cells than immunohistochemistry.

For this test, a sample of cells is treated with special antibodies that stick to the cells only if certain substances are present on their surfaces. The cells are then passed in front of a laser beam. If the cells now have antibodies attached to them, the laser will make them give off light, which can be measured and analyzed by a computer. Groups of cells can be separated and counted by these methods.

This is the most commonly used test for *immunophenotyping* (classifying lymphoma cells according to the substances (antigens) on their surfaces. Different types of lymphocytes have different antigens on their surface. These antigens may also change as each cell matures.

Flow cytometry can help determine whether the lymph node is swollen because of lymphoma, some other cancer, or a non-cancerous disease. It has also become very useful in helping doctors determine the exact type of lymphoma so that they can select the best treatment.

Cytogenetics

This technique allows doctors to evaluate the chromosomes (long strands of DNA) in the lymphoma cells. The cells are looked at under a microscope to see if the chromosomes have any abnormalities. Some lymphoma cells may have too many chromosomes, too few chromosomes, or other changes such as a translocation (where part of one chromosome has broken off and is now attached to another chromosome. These changes can help identify the type of lymphoma.

Cytogenetic testing usually takes about 2 to 3 weeks because the lymphoma cells must grow in lab dishes for a couple of weeks before their chromosomes are ready to be viewed under the microscope.

Molecular genetic tests

These tests look more closely at lymphoma cell DNA. They can detect most changes that are visible by microscope in cytogenetic tests, as well as others that can't be seen. The disadvantage is that they can only be used to look for specific changes, so the doctor has to know what he or she is looking for.

Fluorescent in situ hybridization (FISH): FISH uses special fluorescent dyes that only attach to specific genes or parts of chromosomes. FISH can find most chromosome

changes (such as translocations) that can be seen under a microscope in standard cytogenetic tests, as well as some gene changes too small to be seen with usual cytogenetic testing.

FISH can be used on regular blood or bone marrow samples. It is very accurate and can usually provide results within a couple of days, which is why this test is now used in many medical centers.

Polymerase chain reaction (PCR): PCR is a very sensitive DNA test that can find gene changes and certain chromosome changes too small to be seen with a microscope, even if very few lymphoma cells are present in a sample. .

Blood tests

Blood tests measure the amounts of certain types of cells and chemicals in the blood. They are not used to diagnose lymphoma, but they can sometimes help determine how advanced the lymphoma is.

Patients with known or suspected lymphoma will have a complete blood count (CBC). This test measures the different cells in the blood, such as the red blood cells, the white blood cells, and the platelets. In patients already known to have lymphoma, low blood cell counts can mean that the lymphoma is growing in the bone marrow and affecting new blood cell formation.

Many patients will also have blood chemistry tests run, to look at kidney and liver function. If lymphoma has been diagnosed, another blood test called *lactate dehydrogenase* (LDH) may be checked. LDH levels are often increased in patients with lymphomas.

For some types of lymphoma or if certain treatments may be used, your doctor may also advise you to have other blood tests to see if you have been infected with certain viruses, such as the hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). Infections with these viruses may affect your treatment.

Imaging tests

Imaging tests use x-rays, sound waves, magnetic fields, or radioactive particles to produce pictures of the inside of the body. In someone with known or suspected lymphoma, these tests might be done to look more closely at an abnormal area that might contain lymphoma, to learn how far the lymphoma might have spread, or to find out if treatment has been effective.

Chest x-ray

The chest might be x-rayed to look for enlarged lymph nodes in this area.

Computed tomography (CT) scan

The CT scan is an x-ray test that produces detailed, cross-sectional images of your body. Instead of taking one picture, like a regular x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into an image of a slice of your body.

A CT scanner has been described as a large donut, with a narrow table in the middle opening. You will need to lie still on the table while the scan is being done. CT scans take longer than regular x-rays, and you might feel a bit confined by the ring while the pictures are being taken.

Unlike a regular x-ray, CT scans can show the detail in soft tissues (such as internal organs). This scan can help tell if any lymph nodes or organs in your body are enlarged. CT scans are useful for looking for lymphoma in the abdomen, pelvis, chest, head, and neck.

Before the test, you may be asked to drink a contrast solution and/or get an intravenous (IV) injection of a contrast dye that helps better outline abnormal areas in the body. You may need an IV for the contrast dye injection. The injection can cause some flushing (a feeling of warmth, especially in the face). Some people are allergic and get hives or, rarely, more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor if you have any allergies or have ever had a reaction to any contrast material used for x-rays.

CT-guided needle biopsy: In some cases, CT can be used to guide a biopsy needle into a suspicious area. For this procedure, called a *CT-guided needle biopsy*, you remain on the CT scanning table while a radiologist moves a biopsy needle through the skin and toward the location of the mass. CT scans are repeated until the needle is within the mass. A biopsy sample is then removed to be looked at under a microscope.

Magnetic resonance imaging (MRI) scan

This test is not used as often as CT scans for lymphoma, but if your doctor is concerned about spread to the spinal cord or brain, MRI is very useful for looking at these areas.

Like CT scans, MRI scans provide detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed by the body and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body.

A contrast material called *gadolinium* may be injected into a vein before the scan to better see details. This material is different from what is used for CT scans, so being allergic to one doesn't mean you are allergic to the other. This material should be used with caution (if at all) in people on dialysis (for kidney failure).

MRI scans take longer than CT scans – often up to an hour. You may have to lie inside a narrow tube, which is confining and can be distressing to some people. Newer, more

open MRI machines may be another option. The MRI machine makes loud buzzing and clicking noises that you may find disturbing. Some places provide headphones or earplugs to help block this noise out.

Ultrasound

Ultrasound uses sound waves and their echoes to produce a picture of internal organs or masses. In the most common type of ultrasound, a small, microphone-like instrument called a *transducer* is placed on the skin (which is first lubricated with a gel). It emits sound waves and picks up the echoes as they bounce off the organs. The echoes are converted by a computer into a black and white image that is displayed on a computer screen.

Ultrasound can be used to look at lymph nodes near the surface of the body or to look inside your abdomen for enlarged lymph nodes or organs such as the liver and spleen. It can also detect kidneys that have become swollen because the outflow of urine has been blocked by enlarged lymph nodes. (It can't be used to look at lymph nodes in the chest because the ribs block the sound waves.)

This is an easy test to have done, and it uses no radiation. For most ultrasounds, you simply lie on a table, and a technician moves the transducer over the part of your body being looked at.

Positron emission tomography (PET) scan

For a PET scan, a form of radioactive sugar (known as *fluorodeoxyglucose* or *FDG*) is injected into the blood. Because cancer cells in the body grow rapidly, they absorb large amounts of the radioactive sugar. After about an hour, you will be moved onto a table in the PET scanner. You lie on the table for about 30 minutes while a special camera creates a picture of areas of radioactivity in the body. The picture is not finely detailed like a CT or MRI scan, but it can provide helpful information about your whole body.

- PET scans can help tell if an enlarged lymph node contains lymphoma.
- It can also help spot small areas that might be lymphoma, even if the area looks normal on a CT scan.
- PET scans can be used to tell if a lymphoma is responding to treatment. Some doctors will repeat the PET scan after 1 or 2 courses of chemotherapy. If the chemotherapy is working, the lymph nodes will no longer take up the radioactive sugar.
- PET scans can also be used after treatment in helping decide whether an enlarged lymph node still contains lymphoma or is merely scar tissue.

Often, for patients with lymphoma, a machine that combines the PET scan with a CT scan (PET/CT scan) is used. This lets the doctor compare areas of higher radioactivity on the PET scan with the more detailed appearance of that area on the CT.

Gallium scan

For this test, a solution containing slightly radioactive gallium is injected into a vein. It is attracted to lymph tissue in the body. A few days later a special camera is used to detect the radioactivity, showing the location of the gallium. The gallium scan will not detect most slow-growing lymphomas but will find many fast-growing (aggressive) lymphomas.

This test is not used as much now as in the past, as many doctors may do a PET scan instead. It can still sometimes be useful in finding areas of lymphoma that the PET scan may miss. It can also help distinguish an infection from a lymphoma when the diagnosis is not clear.

Bone scan

For bone scans, a radioactive substance called *technetium* is used. After being injected into a vein, it travels to damaged areas of the bone. Lymphoma often causes bone damage, and a bone scan will find it. But a bone scan may also pick up non-cancerous problems, such as arthritis and fractures.

This test is not usually done unless a person is having bone pain or has lab test results that suggest the lymphoma may have reached the bones.

Tests of heart and lung function

These tests are not used to help diagnose non-Hodgkin lymphoma, but they may be done if you are going to get certain chemotherapy drugs commonly used to treat lymphoma that may affect the heart or the lungs.

- Your heart function may be checked with an echocardiogram (an ultrasound of the heart) or a MUGA scan.
- Your lung function may be checked with pulmonary function tests, in which you breathe into a tube connected to a machine.

How is non-Hodgkin lymphoma staged?

Once non-Hodgkin lymphoma is diagnosed, tests are done to determine the stage (extent of spread) of the disease. The treatment and prognosis (outlook) for a patient with non-Hodgkin lymphoma depend in part on the stage of the lymphoma.

Tests used to gather information for staging include:

- Physical exam
- Biopsies of enlarged lymph nodes or other abnormal areas
- Blood tests

- Imaging tests, such as CT scans
- Bone marrow aspiration and biopsy (often but not always done)
- Lumbar puncture (spinal tap – this may not need to be done)

These tests are described in the section “How is non-Hodgkin lymphoma diagnosed?”

Ann Arbor staging system

A staging system is a way for members of a cancer care team to summarize the extent of a cancer’s spread. The Ann Arbor staging system is most often used to describe the extent of non-Hodgkin lymphoma in adults.

The stages are described by Roman numerals I through IV (1-4). Lymphomas that affect an organ outside the lymph system (an extranodal organ) have E added to their stage (for example, stage IIE), while those affecting the spleen have an S added.

Stage I

Either of the following means the disease is stage I:

- The lymphoma is in only 1 lymph node area or lymphoid organ such as the thymus (I).
- The cancer is found only in 1 area of a single organ outside of the lymph system (IE).

Stage II

Either of the following means the disease is stage II:

- The lymphoma is in 2 or more groups of lymph nodes on the same side of (above or below) the diaphragm (the thin band of muscle that separates the chest and abdomen). For example, this might include nodes in the underarm and neck area but not the combination of underarm and groin nodes (II).
- The lymphoma extends from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.

Stage III

Either of the following means the disease is stage III:

- The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- The cancer may also have spread into an area or organ next to the lymph nodes (IIIE), into the spleen (IIIS), or both (IIISE).

Stage IV

Either of the following means the disease is stage IV:

- The lymphoma has spread outside the lymph system into an organ that is not right next to an involved node.
- The lymphoma has spread to the bone marrow, liver, brain or spinal cord, or the pleura (thin lining of the lungs).

Other modifiers may also be used to describe the lymphoma stage:

Bulky disease

This term is used to describe tumors in the chest that are at least one-third as wide as the chest, or tumors in other areas that are at least 10 centimeters (about 4 inches) across. It is usually designated by adding the letter X to the stage. Bulky disease might need more intensive treatment.

A vs. B

Each stage may also be assigned an A or B. The letter B is added (stage IIIB, for example) if a person has any of the B symptoms listed below:

- Loss of more than 10% of body weight over the previous 6 months (without dieting)
- Unexplained fever of at least 101.5°F
- Drenching night sweats

These symptoms usually mean the disease is more advanced. If a person has any of these, then more intensive treatment is usually recommended. If no B symptoms are present, the letter A is added to the stage.

Small lymphocytic lymphoma (SLL) /chronic lymphocytic leukemia (CLL)

The Ann Arbor system is most often used to stage this lymphoma if it is only in lymph nodes. But if the disease is affecting the blood or bone marrow, it is often staged using the systems for CLL. These systems are described in our document *Leukemia – Chronic Lymphocytic*, in the section “How is chronic lymphocytic leukemia staged?”

Survival rates and factors that affect prognosis (outlook) for non-Hodgkin lymphoma

Survival rates are often used by doctors as a standard way of discussing a person’s prognosis (outlook). Some patients with cancer may want to know the survival statistics for people in similar situations, while others may not find the numbers helpful, or may

even not want to know them. If you do not want to know them, stop reading here and skip to the next section.

The 5-year survival rate refers to the percentage of patients who live at least 5 years after their cancer is diagnosed. Of course, many people live much longer than 5 years (and many are cured).

Five-year *relative* survival rates assume that some people will die of other causes and compare the observed survival with that expected for people without the cancer. This is a better way to see the impact of the cancer on survival.

In order to get 5-year survival rates, doctors have to look at people who were treated at least 5 years ago. Improvements in treatment since then may result in a more favorable outlook for people now being diagnosed with non-Hodgkin lymphoma.

Survival rates are often based on previous outcomes of large numbers of people who had the disease, but they cannot predict what will happen in any particular person's case. Many other factors may affect a person's outlook, such as their other health problems, the type of lymphoma, the stage (extent) of disease at the time of diagnosis, and the treatment received. Certain other factors, which can be grouped as a prognostic index are also important and are discussed below. Your doctor can tell you how the numbers below may apply to you, as he or she is familiar with your particular situation.

The numbers below come from the National Cancer Institute's SEER database, and are based on people diagnosed between 2002 and 2008.

The overall 5-year relative survival rate for people with NHL is 69%, and the 10-year relative survival rate is 59%.

The type and stage of the lymphoma provide useful information about a person's prognosis (outlook), but for some types of lymphomas the stage isn't too helpful on its own. In these cases, other factors can give doctors a better idea about a person's prognosis.

International Prognostic Index

The International Prognostic Index (IPI) was first developed to help doctors determine the outlook for people with fast-growing lymphomas. However, it has proven useful for most other lymphomas as well (other than slow-growing follicular lymphomas, which are discussed below). The index depends on 5 factors:

- The patient's age
- The stage of the lymphoma
- Whether or not the lymphoma is in organs outside the lymph system
- Performance status (PS) – how well a person can complete normal daily activities

- The blood (serum) level of lactate dehydrogenase (LDH), which goes up with the amount of lymphoma in the body

Good prognostic factors	Poor prognostic factors
Age 60 or below	Age above 60
Stage I or II	Stage III or IV
No lymphoma outside of lymph nodes, or lymphoma in only 1 area outside of lymph nodes	Lymphoma is in more than 1 organ of the body outside of lymph nodes
PS: Able to function normally	PS: Needs a lot of help with daily activities
Serum LDH is normal	Serum LDH is high

Each poor prognostic factor is assigned 1 point. People with no poor prognostic factors would have a score of 0, while those with all of the poor prognostic factors would have a score of 5. The index divides people with lymphomas into 4 risk groups:

- Low (0 or 1 poor prognostic factors)
- Low intermediate (2 poor prognostic factors)
- High intermediate (3 poor prognostic factors)
- High (4 or 5 poor prognostic factors)

In the studies used to develop the index, about 75% of people in the lowest risk group lived at least 5 years, whereas only about 30% of people in the highest risk group lived at least 5 years. These numbers show the difference the index scores can make, but the IPI was devised in the early 1990s. Newer treatments have been developed since then, so current survival rates are likely to be higher.

Revised International Prognostic Index

A more recent version of the IPI is based on people with fast-growing lymphomas who have received more modern treatment, including a newer drug called rituximab (Rituxan), which is described in the “Immunotherapy for non-Hodgkin lymphoma” section. The revised IPI uses the same factors but divides patients into only 3 risk groups:

- Very good (no poor prognostic factors)
- Good (1 or 2 poor prognostic factors)
- Poor (3 or more poor prognostic factors)

In the study used to develop this index, about 95% of people in the very good risk group lived at least 4 years, whereas only about 55% of people in the poor risk group lived at least 4 years.

The IPI allows doctors to plan treatment better than they could just based on the type and stage of the lymphoma. This has become more important as new, more effective treatments have been developed that sometimes have more side effects. The index helps doctors figure out whether these treatments are needed.

Follicular Lymphoma International Prognostic Index

The IPI is useful for most lymphomas, but it's not as helpful for follicular lymphomas, which tend to be slower growing. Doctors have developed the Follicular Lymphoma International Prognostic Index (FLIPI) specifically for this type of lymphoma. It uses slightly different prognostic factors than the IPI.

Good prognostic factors	Poor prognostic factors
Age 60 or below	Age above 60
Stage I or II	Stage III or IV
Blood hemoglobin 12 g/dL or above	Blood hemoglobin level below 12 g/dL
4 or fewer lymph node areas affected	More than 4 lymph node areas affected
Serum LDH is normal	Serum LDH is high

Patients are assigned a point for each poor prognostic factor. People without any poor prognostic factors would have a score of 0, while those with all poor prognostic factors would have a score of 5. The index then divides people with follicular lymphoma into 3 groups:

- Low risk: no or 1 poor prognostic factor(s)
- Intermediate risk: 2 poor prognostic factors
- High risk: 3 or more poor prognostic factors

The study used to develop the FLIPI produced the following survival rates:

Risk group	5-year survival rate	10-year survival rate
Low-risk	91%	71%
Intermediate-risk	78%	51%
High-risk	53%	36%

These rates reflect the number of people who lived for *at least* 5 or 10 years after being diagnosed – many people lived longer than this. The rates were based on people

diagnosed with follicular lymphoma in the 1980s and 1990s. Newer treatments have been developed since then, so current survival rates are likely to be higher.

How is non-Hodgkin lymphoma treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of studies published in medical journals, as well as their own professional experience.

The treatment information in this document is not official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor.

Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask him or her questions about your treatment options.

General treatment information

Once non-Hodgkin lymphoma has been diagnosed and staged, your cancer care team will discuss treatment options with you. Several different types of treatment can be used against non-Hodgkin lymphoma. The treatment options depend on the type of lymphoma and its stage (extent), as well as the other prognostic factors. Of course, no 2 patients are exactly alike, and standard options are often tailored to each patient's situation.

The main types of treatment for non-Hodgkin lymphoma are:

- Chemotherapy
- Immunotherapy
- Targeted therapy
- Radiation
- Stem cell transplant

In rare cases, surgery is also used.

Based on your treatment options, you may have different types of doctors on your treatment team. These doctors may include:

- A hematologist: a doctor who treats disorders of the blood, including lymphomas.
- A medical oncologist: a doctor who treats cancer with medicines.
- A radiation oncologist: a doctor who treats cancer with radiation therapy.

Many other specialists may be involved in your care as well, including nurse practitioners, nurses, nutrition specialists, social workers, and other health professionals. Learn more about this in our document *Health Professionals Associated With Cancer Care*.

It's important to discuss all of your treatment options as well as their possible side effects with your doctors to help make the best decision for you. (See the section "What should you ask your doctor about non-Hodgkin lymphoma"). In choosing a treatment plan, consider your health and the type and stage of the lymphoma. Be sure that you understand all the risks and side effects of the various treatments before making a decision. If time permits, it's often a good idea to seek a second opinion. Getting a second opinion can give you more information and help you feel confident about the treatment plan you choose. Your doctor should be willing to help you find another cancer doctor who can give you a second opinion.

The next few sections describe the types of treatment used for non-Hodgkin lymphoma. This is followed by a discussion of the typical treatment options based on the type of lymphoma, stage, and other prognostic factors when these are important.

The "Additional resources for non-Hodgkin lymphoma" section also includes a list of other, more detailed materials on the different types of cancer treatments and their side effects.

Chemotherapy for non-Hodgkin lymphoma

Chemotherapy (chemo) is the use of anti-cancer drugs that are usually injected into a vein or taken by mouth. These drugs enter the bloodstream and reach almost all areas of the body, making this treatment very useful for lymphoma.

Depending on the type and the stage of the lymphoma, chemo may be used alone or combined with radiation therapy.

Doctors give chemo in cycles of a period of treatment, followed by a rest period to allow the body time to recover. Each chemo cycle generally lasts for several weeks. Most chemo treatments are given on an outpatient basis (in the doctor's office or clinic or hospital outpatient department), but some may require a hospital stay.

Many chemo drugs are useful in treating lymphoma patients. Often, several drugs are combined. The number of drugs, their doses, and the length of treatment depend on the type and stage of the lymphoma. Some of the drugs commonly used to treat lymphoma include (divided into groups by how they work):

Alkylating agents

- Cyclophosphamide (Cytosan[®])
- Chlorambucil
- Bendamustine (Treanda[®])
- Ifosfamide (Ifex[®])

Corticosteroids

- Prednisone
- Dexamethasone (Decadron[®])

Platinum drugs

- Cisplatin
- Carboplatin
- Oxaliplatin

Purine analogs

- Fludarabine (Fludara[®])
- [Pentostatin](#) (Nipent[®])
- [Cladribine](#) (2-CdA, Leustatin[®])

Anti-metabolites

- Cytarabine (ara-C)
- Gemcitabine (Gemzar[®])
- Methotrexate
- Pralatrexate (Folotyn[®])

Others

- Vincristine (Oncovin[®])
- Doxorubicin (Adriamycin[®])
- Mitoxantrone
- Etoposide (VP-16)
- Bleomycin

Often drugs from different groups are used in combination. One of the most common combination of drugs is CHOP. This includes the drugs cyclophosphamide, doxorubicin (which has a chemical name beginning with H), vincristine (Oncovin) and prednisone. Another common combination leaves out doxorubicin and is called CVP.

Chemo is often combined with immunotherapy, especially the monoclonal antibody rituximab (Rituxan[®]).

Sometimes a patient may get one chemo combination for several cycles and later switch to a different one if the first combination doesn't seem to be working.

High doses of methotrexate are sometimes used to treat lymphoma in the tissues around the brain and spinal cord and in the spinal fluid (cerebrospinal fluid). More often, though, intrathecal chemo is used.

Intrathecal chemo

Most chemo drugs given systemically (IV or by mouth) cannot penetrate the spinal fluid and tissues around the brain and spinal cord. To treat lymphoma that may have reached these areas, chemo may also be given into the spinal fluid (cerebrospinal fluid). This is called *intrathecal chemo*. The chemo drugs most often used for intrathecal chemo are methotrexate and cytarabine.

Possible side effects

Chemo drugs attack cells that are dividing quickly, which is why they work against lymphoma cells. But other cells in the body, such as those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to certain side effects.

The side effects of chemo depend on the type and dose of drugs given and the length of time they are taken. These side effects can include:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Diarrhea
- Low blood cell counts (see below)

These side effects are usually short-term and go away after treatment is finished. If serious side effects occur, the dose of chemo may be reduced or treatment may be delayed.

There are often ways to lessen these side effects. For example, drugs can be given to prevent or reduce nausea and vomiting.

Certain drugs have specific possible side effects. For example, some drugs cause nerve damage (*neuropathy*), leading to numbness, tingling, or even pain in the hands and feet. Ifosfamide can damage the bladder lining (hemorrhagic cystitis). This can be prevented by giving a drug called *mesna* with ifosfamide.

Other more serious side effects can occur, depending on the chemo drugs used. Drugs such as doxorubicin can damage the heart. Your doctor may order a test of heart function (like a MUGA scan or echocardiogram) before starting you on one of these drugs. Bleomycin can damage lungs. Doctors often test lung function before starting someone on this drug. Many chemo drugs can affect fertility (the ability to have children). Ask your health care team about what side effects you can expect based on the specific drugs you will receive.

Chemo can also cause side effects that might not occur until years after treatment. For example, in rare cases, people may develop leukemia several years later.

Low blood cell counts: Chemo can cause low blood cell counts because it affects the cells that form blood in the bone marrow. This can lead to:

- Increased chance of infections (from low white blood cell counts)
- Easy bruising or bleeding (from low blood platelet counts)
- Fatigue (from low red blood cell counts)

Infections in people getting chemo can be very serious. Drugs known as growth factors (G-CSF or GM-CSF, for example) are sometimes given to help the white blood cells

recover from the effects of chemo and thus reduce the chance of infection. Antibiotics may also be given at the earliest sign of an infection, such as a fever. You also might want to take steps to limit your exposure to germs. These are discussed in our document, *Infections in People With Cancer*.

If your platelet counts are very low, you may be given drugs or platelet transfusions to help protect against bleeding. Fatigue caused by anemia (very low red blood cell counts) can be treated with drugs or with red blood cell transfusions.

Tumor lysis syndrome is a possible side effect of chemo in patients who had large numbers of lymphoma cells in the body before treatment. It occurs most often with the first cycle of chemo. When the cancer cells are killed, they break open and release their contents into the bloodstream. This can overwhelm the kidneys, which cannot get rid of all of these substances at once. This can lead to the build-up of excess amounts of certain minerals in the blood and even kidney failure. The excess minerals can lead to problems with the heart and nervous system. Doctors work to prevent these problems by giving the patient extra fluids and certain drugs, such as sodium bicarbonate, allopurinol, and rasburicase.

More information on chemotherapy and its side effects can be found in the Chemotherapy section of our website, or in our document *A Guide to Chemotherapy*. If you'd like more information on a drug used in your treatment or a specific drug mentioned in this section, see our Guide to Cancer Drugs , or call us with the names of the medicines you're taking.

Other drugs used to treat lymphoma

A certain kind of lymphoma of the stomach, mucosa-associated lymphoid tissue (MALT) lymphoma, is linked to infection with the bacterium *H. Pylori*. Treatment of this infection can cause the lymphoma to go away. This is most often done with a combination of antibiotics along with drugs that turn-off stomach acid called *proton pump inhibitors*. Examples of proton pump inhibitors, include omeprazole (Prilosec[®]), lansoprazole (Prevacid[®]), and esomeprazole (Nexium[®]).

Immunotherapy for non-Hodgkin lymphoma

Immunotherapy is treatment that either boosts the patient's own immune system or uses man-made versions of the normal parts of the immune system. These treatments may kill lymphoma cells or slow their growth.

Monoclonal antibodies

Antibodies are proteins made by the body's immune system to help fight infections. Man-made versions, called *monoclonal antibodies*, can be designed to attack a specific target, such as a substance on the surface of lymphocytes (the cells in which lymphomas start).

Several monoclonal antibodies are now used to treat lymphoma.

Antibodies that target CD20

A number of monoclonal antibody drugs used to treat NHL target the CD20 antigen, a protein found on the surface of B lymphocytes. These include:

- [Rituximab](#) (Rituxan),
- [Obinutuzumab](#) (Gazyva[™]),
- [Ofatumumab](#) (Arzerra[®]), and
- Ibritumomab tiuxetan (Zevalin[®])

Rituximab is often used along with [chemotherapy](#), either as part of the initial treatment or as part of a second-line regimen, but it may also be used by itself.

Obinutuzumab can be used along with the chemo drug chlorambucil as a part of the initial treatment for small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL).

Ofatumumab is used mainly in patients with SLL/CLL that is no longer responding to other treatments such as chemotherapy or other monoclonal antibodies such as alemtuzumab (discussed below).

Ibritumomab tiuxetan is made up of a monoclonal antibody aimed at CD20 that has a radioactive molecule attached to it. The antibody brings radiation directly to the lymphoma cells.

These drugs are infused into a vein (IV), which can take up to several hours depending on the drug. They all can cause side effects during the infusion (while the drug is being given) or several hours afterward. These can be mild, such as itching, chills, fever, nausea, rashes, fatigue, and headaches.

More serious side effects can also occur during the infusion, including chest pain, heart racing, swelling of the face and tongue, cough, trouble breathing, feeling dizzy or light headed, and feeling faint. Because these kinds of reactions are common with obinutuzumab and ofatumumab, drugs to help prevent serious problems will be given before each infusion.

Ibritumomab tiuxetan causes low blood cell counts more often than the other antibodies that target CD20.

All of these drugs can cause hepatitis B infections that were dormant (inactive) to become active again, which can lead to severe liver problems or even death. For that reason, your doctor may check your blood for signs of an old hepatitis infection before starting this drug. If your blood shows signs of an old hepatitis B infection, the doctor will check your blood during treatment to see if the virus becomes active again. If it does, the drug will need to be stopped.

These drugs may also increase a person's risk of certain serious infections for many months after the drug is stopped.

Other side effects can occur depending on which drug is given. Ask your doctor what you can expect.

In rare cases of patients with very high white blood cell counts, some of these drugs may cause a condition called *tumor lysis syndrome* (this was discussed in detail in the [chemotherapy section](#)). This happens when the drug kills the cancer cells so quickly that the body has trouble getting rid of the breakdown products of the dead cells. It generally only occurs during the first course of treatment.

Antibodies targeting CD52

Alemtuzumab (Campath[®]) is an antibody directed at the CD52 antigen. It is useful in some cases of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) and also some types of peripheral T-cell lymphomas. It is infused into a vein (IV), usually 3 times a week for up to 12 weeks. The most common side effects are fever, chills, nausea, and rashes. It can also cause very low white blood cell counts, which increases the risk for serious infections. Antibiotic and antiviral medicines are given to help protect against them, but severe and even life-threatening infections can still occur.

Antibodies that target CD30

Brentuximab vedotin (Adcetris[®]) is an anti-CD30 antibody attached to a chemotherapy drug. Some lymphoma cells have the CD30 molecule on their surface. The antibody acts like a homing signal, bringing the chemo drug to the lymphoma cells, where it enters the cells and causes them to die when they try to divide into new cells.

Brentuximab can be used to treat anaplastic large cell lymphoma (ALCL) that has come back after other treatments. It is infused into a vein (IV) every 3 weeks. Common side effects include nerve damage (neuropathy), low blood counts, fatigue, fever, nausea and vomiting, infections, diarrhea, and cough.

Interferon

Interferon is a hormone-like protein made by white blood cells to help the immune system fight infections. Some studies have suggested that giving man-made interferon can make some types of lymphomas shrink or stop growing.

Common side effects of this treatment include fatigue, fever, chills, headaches, muscle and joint aches, and mood changes. Because of the side effects, interferon is not used very often. It might be given to some patients in addition to chemotherapy.

Immunomodulating agents

These drugs are thought to work against certain cancers by affecting parts of a person's immune system, although exactly how they work isn't clear. They are sometimes used to help treat certain types of lymphoma, usually after other treatments have been tried.

Thalidomide (Thalomid[®]): This drug is mainly used to treat another cancer of the lymphocytes known as multiple myeloma, but it can also be used to treat some types of lymphoma.

Side effects of thalidomide include drowsiness, fatigue, severe constipation, low white blood cell counts (with an increased risk of infection), and neuropathy (painful nerve damage). The neuropathy can be severe, and may not go away after the drug is stopped. There is also an increased risk of serious blood clots (that start in the leg and can travel to the lungs). Because thalidomide causes severe birth defects if taken during pregnancy, the company that makes it puts restrictions on access to it to prevent women who are or might become pregnant from being exposed to it.

Lenalidomide (Revlimid[®]): This is a newer drug that is similar to thalidomide. It may be used to treat some types of lymphoma.

The most common side effects of lenalidomide are low platelet counts (with an increased risk of bleeding) and low white blood cell counts (with an increased risk of infection). It can also cause painful nerve damage. The risk of blood clots isn't as high as with thalidomide, but it is still increased. Like thalidomide, access to lenalidomide is tightly controlled out of concern about possible serious birth defects.

More information on immunotherapy can be found in our document *Immunotherapy*.

Targeted therapy drugs for non-Hodgkin lymphoma

As researchers have learned more about the changes in cells that cause cancer, they have been able to develop newer drugs that specifically target these changes. These drugs are often referred to as *targeted therapy*. These drugs work differently from standard chemotherapy (chemo) drugs and often have different (and less severe) side effects.

Proteasome inhibitors

Proteasome inhibitors work by stopping enzyme complexes (proteasomes) in cells from breaking down proteins important for keeping cell division under control. They are more often used to treat multiple myeloma, but can be helpful in treating some types of non-Hodgkin lymphoma, as well.

Bortezomib (Velcade[®]) is a proteasome inhibitor that is used to treat some lymphomas, usually after other treatments have been tried. Bortezomib is given as an infusion into a vein (IV) or an injection under the skin (sub-q), typically twice a week for 2 weeks, followed by a rest period. Side effects can be similar to those of standard chemo drugs, including low blood counts, nausea, loss of appetite, and nerve damage.

Histone deacetylase (HDAC) inhibitors

HDAC inhibitors are a group of drugs that can affect what genes are active by interacting with a protein in chromosomes called histone.

Romidepsin (Istodax[®]) is an HDAC inhibitor that can be used to treat both peripheral and skin T-cell lymphomas. It is usually given after at least one other treatment has been tried. This drug is given as an IV infusion, usually once a week for 3 weeks in a row, followed by a week off. Side effects tend to be mild, but can include lowered blood cell counts and effects on heart rhythm.

Belinostat (Beleodaq[®]) is another HDAC inhibitor. It is given to treat peripheral T-cell lymphomas, usually after at least one other treatment has been tried. It is given as an IV infusion, usually daily for 5 days in a row, repeated every 3 weeks. Common side effects include nausea, vomiting, tiredness, and low red blood cell counts (anemia).

Kinase inhibitors

Ibrutinib (Imbruvica[®]) is a type of drug known as a kinase inhibitor. It blocks a protein that transmits a signal to some lymphoma cells that helps them grow and survive. It can be used to treat mantle cell lymphoma. This drug is taken by mouth, once a day. Common side effects include diarrhea or constipation, nausea and vomiting, fatigue, swelling, decreased appetite, and low blood counts. Although this drug is approved for use in patients after other treatments have been tried, it is being studied for use earlier in treatment.

Idelalisib (Zydelig[®]) is another kinase inhibitor that can be used to treat NHL, although this one blocks a different kinase (called *PI3K*). This drug has been shown to help treat follicular lymphoma and small lymphocytic lymphoma after other treatments have been tried. It is taken as a pill twice a day. Common side effects include diarrhea, fever, fatigue, nausea, cough, pneumonia, belly pain, chills, rash and low blood counts. Less often, more serious side effects can also occur.

More information about the kinds of drugs considered targeted therapy can be found in our document *Targeted Therapy*.

Radiation therapy for non-Hodgkin lymphoma

Radiation therapy uses high-energy rays to kill cancer cells.

When radiation is used to treat non-Hodgkin lymphoma, it's most often done with a carefully focused beam of radiation, delivered from a machine outside the body. This is known as *external beam radiation*. The treatment is much like getting an x-ray, but the radiation is more intense. The procedure itself is painless. Before the treatments start, the radiation team determines the correct angles for aiming the radiation beams and the proper dose. Each treatment lasts only a few minutes, although the setup time – getting you into place for treatment – usually takes longer. Most often, radiation treatments are given 5 days a week for several weeks.

Radiation can also be given as a drug in some cases (see the section “Immunotherapy for non-Hodgkin lymphoma” for more details).

Radiation might be used as the main treatment for some types of lymphoma if they are found early (stage I or II), because these tumors respond very well to radiation. For more

advanced lymphomas and for some lymphomas that are more aggressive, radiation is sometimes used along with chemotherapy.

People who are getting a stem cell transplant may get radiation to the whole body along with high-dose chemotherapy, to try to kill lymphoma cells throughout the body. For more information, see the section “High-dose chemotherapy and stem cell transplant for non-Hodgkin lymphoma.”

Radiation therapy can also be used to ease (palliate) symptoms caused by lymphoma that has spread to internal organs, such as the brain or spinal cord, or when a tumor is causing pain because it’s pressing on nerves.

Possible side effects

The side effects of radiation therapy depend on where the radiation is aimed. Common side effects include:

- Skin changes similar to sunburn
- Extreme tiredness (fatigue)
- Nausea
- Diarrhea
- Lower blood cell counts

Nausea and diarrhea are more common if the abdomen (belly) is treated with radiation.

Low blood cell counts can lead to problems with:

- Fatigue and weakness (from anemia – too few red blood cells)
- Increased risk of infection (from having too few white blood cells)
- Problems with excess bleeding and easy bruising (from thrombocytopenia – having low platelet counts)

Radiation to the head and neck area can lead to mouth sores and trouble swallowing. Some patients later have problems with dry mouth.

Radiation to the chest can lead to irritation of the esophagus (the tube that connects the throat to the stomach). This can lead to pain swallowing and trouble eating.

Often these effects go away shortly after treatment is finished.

Side effects tend to be worse if radiation and chemotherapy are given together.

Possible long-term side effects of radiation therapy can be more serious.

- Chest radiation therapy may cause lung damage and lead to trouble breathing. It can also affect the heart, making you more likely to have a heart attack later on.

- Radiation to the neck can lead to thyroid problems later in life. This can lead to fatigue and weight gain and is treated with pills containing thyroid hormone. Radiation to the neck may also increase the risk of stroke many years later.
- Side effects of brain radiation therapy usually become most serious 1 or 2 years after treatment and may include headaches and problems such as memory loss, personality changes, and trouble concentrating.
- Other types of cancer can form in the area that received radiation. For example, radiation to the chest may increase the risk of lung cancer (especially in smokers) and of breast cancer. This happens rarely.

More information on radiation therapy can be found in the Radiation Therapy section of our website, or in our document *Understanding Radiation Therapy: A Guide for Patients and Families*.

High-dose chemotherapy and stem cell transplant for non-Hodgkin lymphoma

Stem cell transplants are sometimes used to treat lymphoma patients who are in remission or who have a relapse during or after treatment. Although only a small number of patients with lymphoma are treated with this therapy now, this number is growing.

Stem cell transplants allow doctors to use higher doses of chemotherapy (chemo) to kill the cancer than normally would be tolerated. Radiation is sometimes given as well. This treatment can kill the cancer cells but also destroys the bone marrow, which prevents new blood cells from being formed. This would be fatal if stem cells weren't given back to replace the ones in the bone marrow. The stem cells used for the transplant can come from blood, bone marrow, or umbilical cord blood. In most cases, stem cells from the blood are used.

There are 2 main types of stem cell transplants (SCTs) based on the source of the stem cells. In an autologous SCT, the patient's own stem cells are used. In an allogeneic transplant, the stem cells come from someone else (a donor). The donor's tissue type (also known as the HLA type) needs to match the patient's tissue type as closely as possible to help prevent the risk of major problems with the transplant.

Autologous SCTs are used more often than allogeneic to treat lymphoma. Still, using the patient's own cells may not be an option if the lymphoma has spread to the bone marrow or blood. If that occurs, it may be hard to get a stem cell sample that is free of lymphoma cells.

The use of allogeneic transplants is limited in treating lymphoma because they can have severe side effects that make them hard to tolerate, especially for patients who are older or who have other medical problems. It can also be hard to find a matched donor.

Some patients may be able to be treated with a different type of allogeneic transplant in which lower doses of chemo and radiation are used than in a standard SCT. This is called

a *non-myeloablative transplant (or mini-transplant)*. In this kind of transplant, the chemo and radiation do not completely destroy the lymphoma cells. Instead, they are attacked by the new immune system that comes from the transplanted cells. A non-myeloablative transplant has less severe side effects from the chemo and radiation than a regular allogeneic transplant.

Non-myeloablative transplants are not a standard treatment for lymphoma, but they may help some patients.

Practical points

Bone marrow or peripheral blood SCT is a complex treatment that can cause life-threatening side effects. If the doctors think a patient might benefit from a transplant, it should be done at a hospital where the staff has experience with the procedure and with managing the recovery phase. Some SCT programs may not have experience in certain types of transplants, especially transplants from unrelated donors.

SCT is very expensive (often costing well over \$100,000) and often requires a long hospital stay. Autologous transplant is considered a standard treatment for lymphoma under certain conditions, so most medical insurance will cover the cost. Still, some insurance companies may view other types of SCT as an experimental treatment, and they may not pay for those procedures. Even if the transplant is covered by your insurance, your co-pays may be high. Find out what your insurer will cover before deciding on a transplant so you will have an idea of what you might have to pay.

Possible side effects

The early complications and side effects from a stem cell transplant are basically the same as those caused by any other type chemotherapy (see “Chemotherapy for non-Hodgkin lymphoma”), only they tend to be more severe.

One of the most common and serious short-term effects is the increased risk for infection. Antibiotics are often given to try to keep this from happening. Other side effects, like low red blood cell and platelet counts, may require blood product transfusions or other treatments.

One side effect that occurs is only seen with allogeneic transplants. It is called *graft-versus-host disease*, and it is caused by the donor cells attacking the patient’s own cells and tissues as foreign. This can be very serious and even life-threatening.

Symptoms can include severe skin rashes, itching, mouth sores (which can affect eating), nausea, and severe diarrhea. Liver damage may cause yellowing of the skin and eyes (jaundice). The lungs may also be damaged. The patient may also become easily fatigued and develop muscle aches.

Usually, immune-suppressing drugs can be used to help control GVHD, although they may have their own side effects.

For more information on these procedures, see our document *Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants)*.

Surgery for non-Hodgkin lymphoma

Surgery is often used to get a biopsy sample to diagnose and classify a lymphoma, but it's rarely used as a form of treatment.

In rare cases surgery may be used to treat lymphomas that start in the spleen or in certain organs outside the lymph system, such as the thyroid or stomach, and that have not spread beyond these organs. But for treating lymphoma that's completely confined to one area, radiation therapy is usually preferred over surgery.

For more information about treating cancer with surgery, see our document *A Guide to Cancer Surgery*.

Palliative and supportive care for non-Hodgkin lymphoma

Patients with non-Hodgkin lymphoma (NHL) often benefit from care aimed at helping with problems related to the NHL and its treatment. For example, some patients with NHL have problems with infections or low blood counts. Although treating the NHL may help these over time, other therapies may be needed as well.

Treatments to prevent infections

Antibiotics and anti-virals

Patients getting certain chemotherapy drugs (such as fludarabine and other purine analogs) and the antibody drug alemtuzumab (Campath) have a high risk of infections seen mainly in people with impaired immune systems, like infection with CMV (a virus) and pneumonia caused by *Pneumocystis jirovecii*. An anti-viral drug like acyclovir is often given to try to prevent CMV infections. To help prevent *Pneumocystis pneumonia*, a sulfa antibiotic is often given (trimethoprim with sulfamethoxazole, which is also known by the brand names Septra[®] and Bactrim[®]). Other treatments are available for people who are allergic to sulfa drugs.

Antibiotics and anti-viral drugs are also given to treat infections. Often, active infections require higher doses or different drugs than those used to prevent infections.

Intravenous immunoglobulin (IVIG)

Some patients with NHL have low levels of their own antibodies (immunoglobulins) to fight infection. This can lead to lung and/or sinus infections that keep coming back. The level of antibodies in the blood can be checked with a blood test, and if it is low, antibodies from donors can be given into a vein (IV) to raise the levels and help prevent infections. This is called *intravenous immunoglobulin* or *IVIG*. IVIG is often given once a month at first, but may be able to be given less often based on blood tests of antibody levels.

For more information on infections, see our document *Infections in People With Cancer*.

Treatments for low blood counts

White blood cells, especially a certain kind of white blood cell called the *neutrophil*, are needed to fight infection. Having too few neutrophils (neutropenia) can lead to serious or even life threatening infections. If you become neutropenic from chemotherapy (chemo), you may be treated with injections of a white blood cell growth factor, such as filgrastim (Neupogen[®]) or pegfilgrastim (Neulasta[®]), to boost your neutrophil count. This lowers the risk of serious infections and can allow chemo to continue on time. If you are neutropenic and have signs or symptoms of infection (like a fever), you will be treated with antibiotics.

Some patients develop low red blood cell counts (anemia) from NHL or its treatment. This can lead to patients feeling tired, light headed, or short of breath from walking. Anemia that is causing symptoms can be treated with transfusions. These are often given on an outpatient basis. Drugs that boost red blood cell production can also be used, but these are linked to worse outcomes, and so are generally only used for patients who refuse to have transfusions.

If platelet counts get very low, it can lead to serious bleeding. Transfusing platelets can help prevent this.

In NHL, low red blood and platelet counts can also be caused by the cells being destroyed by abnormal antibodies.

When antibodies lower the numbers of platelets, it is called *immune thrombocytopenia*. Before diagnosing this, the doctor often needs to check the bone marrow to make sure that there isn't another cause for the low platelet counts. In immune thrombocytopenia, giving platelet transfusions doesn't usually help increase the platelet counts much, if at all, because the antibodies just destroy the new platelets, too. This can be treated by drugs that affect the immune system, like corticosteroids and IVIG. Another option is to remove the spleen, since after the antibodies stick to the platelets, they are actually destroyed in the spleen. Another option is treatment with a drug that tells the body to make more platelets, like eltrombopag (Promacta[®]) or romiplostim (Nplate[®]).

When antibodies lower red blood cell counts, it is called *autoimmune hemolytic anemia* (AIHA). This also can be treated with drugs that affect the immune system, like corticosteroids and IVIG. Removing the spleen is also an option. If the patient was being treated with fludarabine (Fludara) when the AIHA developed, the drug may be the cause, and so the fludarabine will be stopped.

Palliative care

Whether your lymphoma is being treated or not, it is important to have treatment to relieve your symptoms. This type of treatment, sometimes called *palliative care*, can be given along with cancer treatment as well as when cancer treatment is no longer working.

Sometimes, the treatments you get to control your symptoms are similar to the treatments used to treat cancer. For example, when lymph nodes become enlarged, they may press on nerves and cause pain. Radiation therapy to these areas may help relieve the pain. Pain medicines, ranging from ibuprofen and similar drugs to more potent medicines such as opioids (like morphine), may also be given.

Nausea and loss of appetite can be treated with drugs and high-calorie food supplements. If the lymphoma has spread to the lungs, patients may get short of breath. Oxygen may be used to help treat this symptom.

It's important that you tell your health care team about any symptoms you have, including any side effects from treatment. There are often ways to help control or lessen these symptoms. This is an important part of your overall treatment plan.

For more information on palliative care and getting help with side effects, see the Palliative or Supportive Care section of our website.

Clinical trials for non-Hodgkin lymphoma

You may have had to make a lot of decisions since you've been told you have cancer. One of the most important decisions you will make is choosing which treatment is best for you. You might have heard about clinical trials being done for your type of cancer, or maybe someone on your health care team has mentioned a clinical trial to you.

Clinical trials are carefully controlled research studies that are done with patients who volunteer for them. They are done to get a closer look at promising new treatments or procedures.

If you would like to take part in a clinical trial, you should start by asking your doctor if your clinic or hospital conducts clinical trials. You can also call our clinical trials matching service for a list of clinical trials that meet your medical needs. You can reach this service at 1-800-303-5691 or on our website at www.cancer.org/clinicaltrials. You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll-free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials website at www.cancer.gov/clinicaltrials.

You must meet requirements to take part in any clinical trial. But if you do qualify for a clinical trial, you still get to decide whether or not to enter (enroll in) it.

Clinical trials are one way to get state-of-the-art cancer treatment. Sometimes they may be the only way to get access to some newer treatments. They are also the only way for doctors to learn better methods to treat cancer. Still, they are not right for everyone.

You can get a lot more information on clinical trials in our document called *Clinical Trials: What You Need to Know*. You can read it on our website or call us to have it sent to you.

Complementary and alternative therapies for non-Hodgkin lymphoma

When you have cancer you are likely to hear about ways to treat your cancer or relieve symptoms that your doctor hasn't mentioned. Everyone from friends and family to social media groups and websites may offer ideas for what might help you. These methods can include vitamins, herbs, and special diets, or other methods such as acupuncture or massage, to name a few.

What exactly are complementary and alternative therapies?

Not everyone uses these terms the same way, and they are used to refer to many different methods, so it can be confusing. We use *complementary* to refer to treatments that are used *along with* your regular medical care. *Alternative* treatments are used *instead of* a doctor's medical treatment.

Complementary methods: Most complementary treatment methods are not offered as cures for cancer. Mainly, they are used to help you feel better. Some methods that are used along with regular treatment are meditation to reduce stress, acupuncture to help relieve pain, or peppermint tea to relieve nausea. Some complementary methods are known to help, while others have not been tested. Some have proven not to be helpful, and a few have even been found harmful.

Alternative treatments: Alternative treatments may be offered as cancer cures. These treatments have not been proven safe and effective in clinical trials. Some of these methods may pose danger, or have life-threatening side effects. But the biggest danger in most cases is that you may lose the chance to be helped by standard medical treatment. Delays or interruptions in your medical treatments may give the cancer more time to grow and make it less likely that treatment will help.

Finding out more

It's easy to see why people with cancer think about alternative methods. You want to do all you can to fight the cancer, and the idea of a treatment with few or no side effects sounds great. Sometimes medical treatments like chemotherapy can be hard to take, or they may no longer be working. But the truth is that most of these alternative methods have not been tested and proven to work in treating cancer.

As you consider your options, here are 3 important steps you can take:

- Look for “red flags” that suggest fraud. Does the method promise to cure all or most cancers? Are you told not to have regular medical treatments? Is the treatment a “secret” that requires you to visit certain providers or travel to another country?
- Talk to your doctor or nurse about any method you are thinking about using.
- Contact us at 1-800-227-2345 to learn more about complementary and alternative methods in general and to find out about the specific methods you are looking at. You

can also check them out in the Complementary and Alternative Medicine section of our website.

The choice is yours

Decisions about how to treat or manage your cancer are always yours to make. If you want to use a non-standard treatment, learn all you can about the method and talk to your doctor about it. With good information and the support of your health care team, you may be able to safely use the methods that can help you while avoiding those that could be harmful.

Treating B-cell non-Hodgkin lymphoma

Treatment usually depends both on the type of lymphoma and the extent of the disease in the body. Other factors may be important as well. If you'd like more information on a drug used in your treatment or a specific drug mentioned in this section, see our Guide to Cancer Drugs , or call us with the names of the medicines you're taking.

Diffuse large B-cell lymphoma

In most cases, the treatment for diffuse large B-cell lymphoma (DLBCL) is chemotherapy (chemo), usually with a regimen of 4 drugs known as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), plus the monoclonal antibody rituximab (Rituxan). This regimen, known as R-CHOP, is most often given in cycles 3 weeks apart.

Stage I or II

For DLBCL that is localized to 1 or 2 lymph node groups on the same side of the diaphragm, R-CHOP may be given for 3 cycles, followed by radiation therapy to the lymph node areas involved by lymphoma. If the lymphoma mass is large, R-CHOP may be given for 6 cycles, and radiation isn't always needed.

Stage III or IV

Most doctors will give 6 cycles of R-CHOP as first-line treatment. Because CHOP contains the drug doxorubicin, which can damage the heart, this regimen may not be suitable for patients with heart problems. In those patients, other chemo regimens may be used instead. People with lymphoma in certain locations (such as the sinuses, testicles, or bone marrow) have a higher risk of the lymphoma coming back later in the tissues around the brain and spinal cord. To prevent that, these patients may be treated with chemo injected into the spinal fluid (called *intrathecal chemotherapy*). Another option is to give high doses of methotrexate intravenously (this drug can pass into the spinal fluid).

Some studies have suggested that for younger patients with a high International Prognostic Index (IPI) score, high-dose chemo followed by an autologous stem cell transplant may be better than chemo alone. But it's not yet clear if transplants are better

as the initial treatment. Most doctors feel that if a transplant is done as part of the first treatment, it should be done in a clinical trial.

If the lymphoma doesn't go away completely with treatment or if it recurs (comes back) after treatment, doctors will usually suggest another chemo regimen. Several different regimens can be used, and they may or may not include rituximab. If the lymphoma shrinks with this treatment, it is followed by high-dose chemo and a stem cell transplant if possible, as it offers the best chance of curing the lymphoma. Stem cell transplants are not effective unless the lymphoma responds to chemo. Unfortunately, not everyone is in good enough health to have a stem cell transplant. Clinical trials of new treatments may be another good option for some people.

Diffuse large B-cell lymphoma can be cured in about half of all patients, but the stage of the disease and the IPI score can have a large effect on this. Patients with lower disease stages have better survival rates, as do patients with lower IPI scores.

Primary mediastinal B-cell lymphoma

This lymphoma is treated like a localized diffuse large B-cell lymphoma. The main treatment is usually about 6 courses of CHOP chemo plus rituximab (R-CHOP). This may be followed by radiation to the mediastinum. Often a PET/CT scan is done after the chemo to see if there's any lymphoma remaining in the chest. If no active lymphoma is seen on the PET/CT, the patient may be observed without further treatment. If the PET/CT scan is positive (shows possible active lymphoma), radiation may be needed. Often, the doctor will order a biopsy of the chest tumor to confirm that lymphoma is still present before starting radiation.

Follicular lymphoma

This type of lymphoma is often slow growing and responds well to treatment, but it is very hard to cure. It is common for this lymphoma to come back after treatment, although it can take years to do so. In many cases, it is not clear that treating the lymphoma right away helps people live longer. Because of this, some doctors recommend no treatment until the lymphoma has begun to cause problems other than mildly swollen lymph nodes. Some patients may never need treatment at all. In those that do, it can take years before treatment is needed.

Stage I and early-stage II

For follicular lymphoma that is only in 1 lymph node group or in 2 nearby groups on the same side of the diaphragm, the preferred treatment is radiation therapy to the lymph node areas affected by lymphoma (this is called *involved field radiation*). Other choices include treatment with rituximab (Rituxan), chemo, or both (together).

Stages III, IV, and more advanced stage II

The most common treatment is rituximab combined with chemo. The chemo can be a single drug (such as bendamustine or fludarabine) or a combination of drugs, such as the

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, vincristine, prednisone) regimens. If the lymphoma shrinks, a total of 6 cycles of chemo plus rituximab is usually given. Other options for initial treatment include rituximab alone or chemo alone (either one or several drugs). If some lymph nodes are very large from the lymphoma, radiation may be used to reduce symptoms. This is most often used for patients who are too sick to be treated with chemo.

The radioactive monoclonal antibody ibritumomab (Zevalin) is also an option for initial treatment, although this is more often used as a second-line treatment.

For patients who may not be able to tolerate more intensive chemo regimens, rituximab alone, milder chemo drugs (such as chlorambucil or cyclophosphamide), or both may be good options.

If the lymphoma shrinks or goes away with the initial treatment, doctors may advise either close follow-up or further treatment. This might include either rituximab for up to 2 years or treatment with ibritumomab. Further treatment may lower the chance that the lymphoma will come back later and may help some patients live longer, but it can also have side effects.

If follicular lymphoma doesn't respond to the initial treatment or if it comes back later, it may be treated with different chemo drugs, targeted drugs, monoclonal antibodies, or some combination of these. If the lymphoma responds to this treatment, a stem cell transplant may be an option.

In some cases, follicular lymphoma can change (transform) into or return as diffuse large B-cell lymphoma. When this happens, the treatment is the same as for this more aggressive disease.

Small lymphocytic lymphoma (and chronic lymphocytic leukemia)

Small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL) are considered different versions of the same disease. The main difference is where the cancer cells are – the blood and bone marrow for CLL and the lymph nodes and spleen for SLL. CLL and SLL tend to grow slowly, but are very hard to cure.

Treatment for SLL is similar to that of CLL, which is described in detail our document *Leukemia -- Chronic Lymphocytic*.

If the lymphoma isn't growing quickly or causing any problems, it can be watched closely without treatment for a time.

If treatment is needed, it depends on the stage. When the lymphoma is only in one lymph node or lymph node area (Ann Arbor stage I), it may be treated with radiation treatment alone.

For more advanced disease, the treatment is often the same as what is used for CLL (this is discussed in detail in our document *Leukemia -- Chronic Lymphocytic*). Chemo, with

or without rituximab or obinutuzumab (Gazyva) is the usual first-line treatment. Chlorambucil, fludarabine, or bendamustine are some of the chemo drugs that are used. Another option is to give rituximab alone (without chemo). Which treatment is used depends on the age and health of the patient, as well as on whether the cancer cells have certain chromosome changes.

If the lymphoma doesn't respond or comes back after initial treatment, different chemo drugs, targeted drugs, and/or other monoclonal antibodies may be used as second-line treatment.

Mantle cell lymphoma

This type of lymphoma is very hard to cure. It has often spread widely when it's first found, and although it doesn't usually grow as quickly as some other fast-growing lymphomas like Burkitt lymphoma, it often doesn't respond as well to treatment, either. Because current treatments for this type of lymphoma are very unlikely to cure it, patients might want to consider taking part in a clinical trial.

If the lymphoma has only spread to 1 lymph node group or to 2 nearby groups on the same side of the diaphragm (stage I and some stage II – which is rare), it can sometimes be treated with radiation therapy. Another option is to treat with chemo plus rituximab.

Cases of mantle cell lymphoma that are more widely spread when they are first diagnosed are treated with chemo plus rituximab. When possible, the chemo treatment is intense, such as

- Hyper-CVAD: cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone, alternating with high-dose methotrexate plus cytarabine).
- “Dose-intensified” CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) alternating with rituximab and cytarabine.
- CHOP plus rituximab followed by rituximab plus ifosfamide, carboplatin, and etoposide (known as ICE)

Less intense chemo regimens may be used for people who are older or who have other health issues.

For those whose lymphoma responds well to initial treatment, a stem cell transplant may be a good option.

For mantle cell lymphomas that don't respond or that come back after initial treatment, chemo with drugs such as bendamustine, bortezomib (Velcade), cladribine, fludarabine, lenalidomide (Revlimid), or ibrutinib (Imbruvica) may be used, sometimes along with other chemo drugs or with rituximab. Still, because the outlook for patients with these lymphomas is poor with second-line treatment (treatment given after the first treatment didn't work), they should consider entering a clinical trial.

Extranodal marginal zone B-cell lymphoma – mucosa-associated lymphoid tissue (MALT) lymphoma

The most common type, gastric (stomach) MALT lymphoma, often occurs as a result of a chronic infection with the bacterium, *H. pylori* and can respond if the infection is treated. Because of this, gastric lymphomas are treated differently from other lymphomas in this group.

Stages I and II in people who tested positive for H. pylori:

Early-stage gastric MALT lymphomas, are treated with antibiotics combined with drugs that block acid secretion by the stomach called proton pump inhibitors. Usually the drugs are given for 10 to 14 days. This may be repeated after a couple of weeks. Examination of the stomach lining using upper endoscopy (where a flexible tube with a viewing lens is passed down the throat through the esophagus and into the stomach) is then repeated at certain intervals to see if the *H. pylori* is gone and if the lymphoma has decreased in size. About 2 out of 3 of these lymphomas go away completely with antibiotic treatment, but it can sometimes take several months to be effective. In cases where symptoms need to be relieved before the antibiotics take effect or where antibiotics don't shrink the lymphoma, radiation therapy to the area is often the preferred treatment. The monoclonal antibody rituximab may be another option.

Stages I and II in people who test negative for H. pylori

For these early-stage gastric MALT lymphomas, treatment is usually either radiation therapy to the stomach or rituximab.

Stage III or IV

For more advanced gastric MALT lymphomas, which are rare, treatment is often similar to that for follicular lymphoma (see above). Lymphomas that are not growing quickly may be watched and not treated right away. If the lymphoma is large, is causing symptoms, or is growing, it can be treated with radiation therapy to the stomach, rituximab, chemo, or chemo plus rituximab. The drugs used are the same as those used for follicular lymphoma, and may include single agents such as chlorambucil or fludarabine or combinations such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, vincristine, prednisone).

For MALT lymphomas that start in sites other than the stomach (non-gastric lymphomas), treatment depends on the location of the lymphoma and how much it has spread. Early-stage lymphomas can often be treated with radiation to the area containing the lymphoma. In certain sites (such as the lungs, breast, or thyroid), surgery may be an option. For more advanced disease (stage III or IV), treatment is generally the same as for stage III and IV gastric MALT lymphoma and follicular lymphoma (see above).

Nodal marginal zone B-cell lymphoma

This rare type of lymphoma generally grows slowly. Like follicular lymphoma, it often does not need to be treated at first. If treatment is needed, what is used depends upon the stage of the lymphoma.

Stage I and early-stage II

If the lymphoma is only in 1 lymph node group or in 2 nearby groups on the same side of the diaphragm, the preferred treatment is radiation therapy to the lymph node areas affected by lymphoma (this is called *involved field radiation*). Other choices include treatment with rituximab (Rituxan), chemo, or both (together).

Stages III, IV, and more advanced stage II:

The most common initial treatment is rituximab combined with chemo. The chemo can be a single chemo drug (such as bendamustine or fludarabine) or a combination of drugs, such as the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, vincristine, prednisone) regimens. If the lymphoma shrinks, a total of 6 cycles of chemo plus rituximab is usually given.

Other options for initial treatment include rituximab alone or chemo alone (either one or several drugs). If some lymph nodes are very large from the lymphoma, radiation may be used to reduce symptoms. This is most often used for patients who are too sick to be treated with chemo.

The radioactive monoclonal antibody ibritumomab tiuxetan (Zevalin) is also an option for initial treatment, although this is more often used as a second treatment.

For patients who may not be able to tolerate more intensive (stronger) chemo regimens, rituximab alone, milder chemo drugs (such as chlorambucil or cyclophosphamide), or both may be good options.

If the lymphoma shrinks or goes away with the initial treatment, doctors may advise either close follow-up or further treatment. This might include either rituximab for up to 2 years or treatment with ibritumomab tiuxetan. Further treatment may lower the chance that the lymphoma will come back later and may help some patients live longer, but it can also have side effects.

If the lymphoma doesn't respond to the initial treatment or if it comes back later, it may be treated with different chemo drugs, monoclonal antibodies, or some combination of these. If the lymphoma responds to this treatment, a stem cell transplant may be an option.

Nodal marginal zone B-cell lymphoma can also change into a fast-growing large cell lymphoma, which would require more aggressive chemotherapy.

Splenic marginal zone B-cell lymphoma

This is also a slow-growing lymphoma. If it is not causing symptoms, it is often watched closely without treating it right away. For a patient with chronic hepatitis C virus infection, treating the infection with interferon with or without anti-viral drugs can cause the lymphoma to go into remission.

If that doesn't work and for people who aren't infected with hepatitis C, removing the spleen with surgery can sometimes lead to a long-term remission of the disease. This can be very helpful in relieving symptoms if the spleen is enlarged. Treatment with rituximab may be another option.

If the disease is more advanced or progresses, it's usually treated with chemo with or without rituximab.

Sometimes this lymphoma can transform into an aggressive large-cell lymphoma, which then requires more intensive chemo.

Burkitt lymphoma

This is a very fast-growing lymphoma that is similar to a type of acute lymphocytic leukemia. It is usually treated in the hospital with intensive chemo. Most regimens for this disease include at least 5 chemo drugs. Many regimens also include a steroid drug such as prednisone or dexamethasone. Rituximab may also be added. Some examples of chemo regimens used for this lymphoma include:

- Hyper-CVAD: cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone, alternating with methotrexate and cytarabine (ara-C)
- CODOX-M/IVAC: cyclophosphamide, vincristine (Oncovin), doxorubicin, and high-dose methotrexate, alternating with ifosfomide, etoposide (VP-16), and cytarabine (ara-C).
- EPOCH: etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, and doxorubicin

Because this lymphoma tends to invade the area around the brain and spinal cord, the chemo drug methotrexate is often given into the spinal fluid (this is called *intrathecal therapy*). This may not be needed if high-dose methotrexate is given as a part of systemic chemotherapy.

An important part of the initial treatment of this disease is making sure these patients get plenty of fluids and drugs like allopurinol to help prevent tumor lysis syndrome (described in the "Chemotherapy for non-Hodgkin lymphoma" section).

If the lymphoma doesn't respond or comes back after treatment, other chemo may be tried. If the lymphoma goes into remission, the doctor might suggest a stem cell transplant.

Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)

The main treatment for this lymphoma is usually chemo or rituximab. For more detailed information see our document *Waldenstrom Macroglobulinemia*.

Hairy cell leukemia

This is a slow-growing lymphoma that tends to invade the spleen and lymph nodes as well as the blood. Patients without symptoms often don't need to be treated right away. When treatment is needed, most often the chemo drugs cladribine (2-CdA) or pentostatin are used. For more detailed information see our document *Leukemia: Chronic Lymphocytic*.

Primary central nervous system (CNS) lymphoma

This lymphoma begins in the brain or spinal cord. It often develops in older people or those with immune system problems caused by AIDS or drugs given to keep transplanted organs from being rejected.

Most patients are treated with chemo and/or radiation. One problem with treating this disease is that most chemo drugs commonly used to treat lymphoma don't reach the brain when given intravenously (IV). For people in reasonably good health, high IV doses of the drug methotrexate have been shown to be the most effective treatment. This is given along with the drug leucovorin and IV fluids, which help limit serious side effects. Other chemo drugs, such as cytarabine, may be added. Rituximab may be added as well. For those who aren't able to tolerate this treatment, other, less intensive chemo regimens or radiation therapy alone may be tried.

One problem with radiation therapy, especially in older patients, is that it often causes mental changes. Doctors limit the dose of radiation to try to lessen this problem.

If CNS lymphoma keeps growing or comes back after treatment, further options may include chemo (using different drugs), radiation therapy, or a stem cell transplant if a person is healthy enough.

Historically, the outlook for patients with primary CNS lymphoma has not been as good as for other lymphomas, but this is at least partly related to the fact that they tend to be older or have other serious health problems.

Treatment of lymphoma of the eye (primary intraocular lymphoma) is discussed in our document, *Eye Cancer (Melanoma and Lymphoma)*.

Treating T-cell non-Hodgkin lymphomas

Precursor T-lymphoblastic lymphoma/leukemia

This disease can occur in both children and adults and it can be considered either a lymphoma or leukemia.

It's considered a lymphoma if there are tumor masses and if cancer (lymphoma) cells make up less than 25% of the bone marrow. This is a fast-growing disease that's treated with intensive chemo when possible.

The treatment for the lymphoma form of this disease is similar to that used for the leukemia form, which is discussed in more detail in our documents, *Leukemia--Acute Lymphocytic (Adults)* and *Childhood Leukemia*.

Combinations of many drugs are used. These can include cyclophosphamide, doxorubicin (Adriamycin), vincristine, L-asparaginase, methotrexate, prednisone, and, sometimes, cytarabine (ara-C). Because of the risk of spread to the brain and spinal cord, a chemo drug such as methotrexate is also given into the spinal fluid. Some doctors suggest maintenance chemo for up to 2 years after the initial treatment to reduce the risk of recurrence. High-dose chemo followed by a stem cell transplant may be another option.

During the initial treatment, patients are at risk for tumor lysis syndrome (described in the "Chemotherapy for non-Hodgkin lymphoma" section), and so are given plenty of fluids and drugs like allopurinol.

Although this lymphoma is fast-growing, if it hasn't spread to the bone marrow when it's first diagnosed, the chance of cure with chemo is quite good. But once it has spread to the bone marrow, only about 40% to 50% of patients can be cured.

Peripheral T-cell lymphomas

Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome, and others)

Treatment of these skin lymphomas is discussed in our document *Lymphoma of the Skin*.

Adult T-cell leukemia/lymphoma

There are 4 subtypes of this lymphoma, and treatment depends on which subtype you have.

The smoldering and chronic subtypes grow slowly. Like other slow-growing lymphomas (such as follicular lymphoma and small lymphocytic lymphoma), these subtypes are watched without treatment as long as they aren't causing problems other than mildly swollen lymph nodes. If treatment is needed, one option is treatment with interferon and zidovudine to fight the HTLV-1 virus. If the lymphoma is affecting the skin, it may be

treated with radiation. Another option is chemo, using CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other combinations.

The acute and lymphoma subtypes also can be treated with either antiviral drugs or chemo. Some doctors feel that the acute subtype responds better to antiviral drugs, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) is the most common chemo combination used.

The lymphoma subtype can involve the tissues around the brain and spinal cord, so chemo is also given into the spinal fluid (intrathecal chemo). Treatment after chemo may include an allogeneic stem cell transplant. Because there is no clear standard treatment for this disease, patients should consider enrolling in a clinical trial if one is available.

Angioimmunoblastic T-cell lymphoma

This fast-growing lymphoma is often first treated with steroids (such as prednisone or dexamethasone) alone, especially in older patients who would have trouble tolerating chemo. This treatment can reduce fever and weight loss, but the effect is often temporary. If chemo is needed, combinations such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) may be used.. If the lymphoma is only in one area, radiation therapy may be an option.

Chemo rarely produces long-term remissions, so a stem cell transplant is often suggested after initial chemotherapy if a person can tolerate it.

Extranodal natural killer/T-cell lymphoma, nasal type

This rare lymphoma is often confined to the nasal passages. Patients with stage I disease who do not have any poor risk factors, such as being 60 years or older in age, having B symptoms, or certain lab values, such as a high LDH (lactate dehydrogenase) or Epstein-Barr virus level, may be treated with radiation therapy alone. Patients with more advanced stage disease or stage I with poor risk factors can be treated with chemoradiation (chemo and radiation given together), chemo followed by radiation, or chemo alone.

When chemoradiation is given, it may be cisplatin with radiation followed by chemo with VIPD (etoposide, ifosfamide, carboplatin and dexamethasone). Another option is radiation with DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin).

If chemo is given before radiation, often DeVIC or SMILE (methotrexate, dexamethasone, ifosfamide, leucovorin, etoposide, and L-asparaginase).

SMILE or AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) are options if chemo is given without radiation.

If the lymphoma doesn't go away completely, a stem cell transplant may be done if possible.

Enteropathy-associated T-cell lymphoma

This lymphoma generally develops in the small intestine or colon. Chemo using several drugs is usually the main treatment. Often CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the chemo used. If the lymphoma is only in one area, radiation therapy may be used as well. But if these treatments work, a hole (perforation) can develop in the intestines (as the lymphoma cells die), so often surgery to remove the part of the intestines containing the lymphoma is done first. Surgery may also be needed before chemo or radiation if the patient is diagnosed with this lymphoma because it caused a perforation or intestinal blockage (obstruction). A stem cell transplant may be an option if the lymphoma responds to chemo.

Anaplastic large cell lymphoma

This fast-growing lymphoma mainly affects lymph nodes and is treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), or some other chemo regimens. Doctors might recommend radiation therapy as well for some patients.

This lymphoma often responds well to treatment, and long-term survival is common, especially if the lymphoma cells stain positive for the ALK protein. If the cells lack the ALK protein or if the lymphoma returns after initial treatment, an autologous stem cell transplant may be an option. Another option for lymphomas that no longer respond to initial treatment is the labeled monoclonal antibody brentuximab vedotin (Adcetris).

For anaplastic large cell lymphoma associated with a breast implant, experts recommend removing the implant and the capsule surrounding it (that contains the lymphoma). Additional treatment may include chemo, sometimes with radiation.

Peripheral T-cell lymphoma, unspecified

These lymphomas are generally treated the same way as diffuse large B-cell lymphomas. Chemo with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other drug combinations is used. For early-stage disease, radiation therapy may be added. Stem cell transplants may be recommended as part of the treatment when possible.

If other treatments are no longer working, newer chemo drugs such as pralatrexate (Folotyn), targeted drugs such as bortezomib (Velcade), belinostat (Beleodaq), or romidepsin (Istodax), or immunotherapy drugs such as alemtuzumab (Campath) and denileukin diftitox (Ontak) may be tried.

The outlook is usually not as good as in diffuse B-cell lymphoma, so taking part in a clinical trial of newer treatments is often a good option.

Treating HIV-associated lymphoma

People with HIV infections are at increased risk for lymphoma. Although people with HIV often have aggressive forms of lymphoma such as diffuse large B-cell lymphoma, primary CNS lymphoma, or Burkitt lymphoma, their outlook has improved a great deal in recent years. The use of highly active anti-retroviral therapy (HAART) to treat HIV has helped patients to better tolerate treatments such as chemo and immunotherapy.

The major problem in the past was that patients with HIV infection tended to have low blood cell counts to begin with, which made it hard to treat them with full doses of chemo. This problem has been relieved somewhat by the use of HAART and by the use of drugs to help the patient's body make new blood cells. Still, doctors give chemo cautiously and monitor blood counts closely. HIV can lower the number of a certain white blood cell, the CD4 cell. Since, patients with low CD4 counts can have more problems when treated with rituximab, some experts omit this drug in patients who have low CD4 counts.

Most experts believe that the prognosis (outlook) for a person with HIV-associated lymphoma relates at least as much to the HIV infection as to the lymphoma. Modern anti-HIV therapy can often control the immune deficiency in patients with AIDS, so the outlook for those patients who develop lymphoma has improved. The treatment of the lymphoma itself depends on the specific type of lymphoma.

More treatment information for non-Hodgkin lymphoma

For more details on treatment options – including some that may not be addressed in this document – the National Comprehensive Cancer Network (NCCN) and the National Cancer Institute (NCI) are good sources of information.

The NCCN, made up of experts from many of the nation's leading cancer centers, develops cancer treatment guidelines for doctors to use when treating patients. These are available on the NCCN website (www.nccn.org).

The NCI provides treatment guidelines via its telephone information center (1-800-4-CANCER) and its website (www.cancer.gov). Detailed guidelines intended for use by cancer care professionals are also available on www.cancer.gov.

What should you ask your doctor about non-Hodgkin lymphoma?

It's important to have frank, open discussions with your cancer care team. They want to answer all of your questions, no matter how minor they might seem. For instance, consider asking these questions:

- What kind of non-Hodgkin lymphoma do I have?
- Has my biopsy been reviewed by a pathologist who's an expert on lymphoma?

- Are there other tests that need to be done before we can decide on treatment?
- Are there other doctors I need to see?
- What's the stage (extent) of the lymphoma, and what does that mean in my case?
- What's my International Prognostic Index (IPI) score, and does it affect my options?
- How much experience do you have treating this type of lymphoma?
- Should I get a second opinion before starting treatment? Can you suggest someone?
- What are my treatment options? Do we need to treat the lymphoma right away?
- What do you recommend, and why?
- What risks or side effects are there to the treatments you suggest?
- What should I do to be ready for treatment?
- How long will treatment last? What will it involve? Where will it be done?
- How will treatment affect my daily activities?
- What's my outlook for survival?
- What are the chances of the lymphoma coming back with these treatment plans?
- What would we do if the treatment doesn't work or if the lymphoma comes back?
- What type of follow-up will I need after treatment?

Along with these sample questions, be sure to write down some of your own. For instance, you might want more information about recovery times so that you can plan your work or activity schedule. Or you may want to ask about clinical trials for which you qualify. You can find more information about communicating with your health care team in our document *Talking With Your Doctor*.

What happens after treatment for non-Hodgkin lymphoma?

For many people with non-Hodgkin lymphoma, treatment may remove or destroy the cancer. Completing treatment can be both stressful and exciting. You may be relieved to finish treatment, but find it hard not to worry about the lymphoma growing or coming back. (When cancer comes back after treatment, it is called *recurrence*.) This is a very common concern in people who have had cancer.

It may take a while before your fears lessen. But it may help to know that many cancer survivors have learned to live with this uncertainty and are leading full lives. Our

document *Living With Uncertainty: The Fear of Cancer Recurrence*, gives more detailed information on this.

For some people, the lymphoma may never go away completely. These people may get regular treatments with chemo, radiation, or other therapies to help keep the lymphoma in check for as long as possible. Learning to live with lymphoma as more of a chronic disease can be difficult and very stressful. It has its own type of uncertainty. Our document *When Cancer Doesn't Go Away* talks more about this

Follow-up care

Lymphomas are a diverse group of diseases that require different treatments and can have very different prognoses (outlooks). Your care after treatment will depend to a large extent on the type of lymphoma you have, what type of treatment you received, and how well treatment worked.

If you have completed treatment, your doctors will still want to watch you closely. It's very important to go to all of your follow-up appointments. During these visits, your doctors will ask about any problems you may have, examine you, and may order lab tests or imaging tests such as CT or PET/CT scans to look for signs of cancer or treatment side effects.

Almost any cancer treatment can have side effects. Some may last for a few weeks to months, but others can last the rest of your life. This is the time for you to talk to your cancer care team about any changes or problems you notice and any questions or concerns you have.

Follow-up tests

Your doctor will probably want to see you regularly, usually every few months for the first year or so and gradually less often after that. Your physical exam will include careful attention to size and firmness of lymph nodes.

Imaging tests may be done, based on the type, location, and stage of lymphoma. If internal lymph nodes or other internal organs are or were affected, CT scans or PET/CT scans may be used to measure the size of any remaining tumor masses.

You may need to have frequent blood tests to check that you have recovered from treatment and to look for possible signs of problems such as lymphoma recurrence. Blood counts can also sometimes become abnormal because of a disease called *myelodysplasia*, which is a defect of the bone marrow that can lead to leukemia. Some chemotherapy drugs can cause this disease. For more on this, see our document *Myelodysplastic Syndromes*. It's also possible for a person to develop leukemia a few years after being treated for lymphoma.

It's also important to keep your health insurance. Tests and doctor visits cost a lot, and even though no one wants to think of their cancer coming back, this could happen.

If the lymphoma does come back at some point, further treatment will depend on what treatments you've had before, how long it's been since treatment, and your overall health (see the section "If treatment for non-Hodgkin lymphoma stops working"). For more general information on dealing with a recurrence, see our document *When Your Cancer Comes Back: Cancer Recurrence*.

Seeing a new doctor

At some point after your cancer diagnosis and treatment, you may find yourself seeing a new doctor who doesn't know anything about your medical history. It's important that you be able to give your new doctor the details of your diagnosis and treatment. Make sure you have this information handy:

- A copy of your pathology report(s) from any biopsies or surgeries
- Copies of imaging tests (CT or MRI scans, etc.), which can usually be stored on a CD, DVD, etc.
- If you had surgery, a copy of your operative report(s)
- If you were in the hospital, a copy of the discharge summary that doctors prepare when patients are sent home
- If you had drug treatment (such as chemotherapy, targeted therapy, or immunotherapy), a list of the drugs, drug doses, and when you took them
- If you had radiation therapy, a summary of the type and dose of radiation and when and where it was given

The doctor may want copies of this information for his records, but always keep copies for yourself.

Lifestyle changes after treatment for non-Hodgkin lymphoma

You can't change the fact that you have had cancer. What you can change is how you live the rest of your life – making choices to help you stay healthy and feel as well as you can. This can be a time to look at your life in new ways. Maybe you are thinking about how to improve your health over the long term. Some people even start during cancer treatment.

Making healthier choices

For many people, a diagnosis of cancer helps them focus on their health in ways they may not have thought much about in the past. Are there things you could do that might make you healthier? Maybe you could try to eat better or get more exercise. Maybe you could cut down on alcohol, or give up tobacco. Even things like keeping your stress level under control may help. Now is a good time to think about making changes that can have positive effects for the rest of your life. You will feel better and you will also be healthier.

You can start by working on those things that worry you most. Get help with those that are harder for you. For instance, if you are thinking about quitting smoking and need help, call the American Cancer Society at 1-800-227-2345.

Eating better

Eating right can be hard for anyone, but it can get even tougher during and after cancer treatment. Treatment may change your sense of taste. Nausea can be a problem. You may not feel like eating and lose weight when you don't want to. Or you may have gained weight that you can't seem to lose. All of these things can be very frustrating.

If treatment caused weight changes or eating or taste problems, do the best you can and keep in mind that these problems usually get better over time. You may find it helps to eat small portions every 2 to 3 hours until you feel better. You may also want to ask your cancer team about seeing a dietitian, an expert in nutrition who can give you ideas on how to deal with these treatment side effects.

One of the best things you can do after cancer treatment is put healthy eating habits into place. You may be surprised at the long-term benefits of some simple changes, like increasing the variety of healthy foods you eat. Getting to and staying at a healthy weight, eating a healthy diet, and limiting your alcohol intake may lower your risk for a number of types of cancer, as well as having many other health benefits. Get more information in our document *Nutrition and Physical Activity During and After Cancer Treatment: Answers to Common Questions*.

Rest, fatigue, and exercise

Extreme tiredness, called *fatigue*, is very common in people treated for cancer. This is not a normal tiredness, but a “bone-weary” exhaustion that doesn't get better with rest. For some people, fatigue lasts a long time after treatment, and can make it hard for them to exercise and do other things they want to do. But exercise can help reduce fatigue. Studies have shown that patients who follow an exercise program tailored to their personal needs feel better physically and emotionally and can cope better, too.

If you were sick and not very active during treatment, it is normal for your fitness, endurance, and muscle strength to decline. Any plan for physical activity should fit your own situation. An older person who has never exercised will not be able to take on the same amount of exercise as a 20-year-old who plays tennis twice a week. If you haven't exercised in a few years, you will have to start slowly – maybe just by taking short walks.

Talk with your health care team before starting anything. Get their opinion about your exercise plans. Then, try to find an exercise buddy so you're not doing it alone. Having family or friends involved when starting a new exercise program can give you that extra boost of support to keep you going when the push just isn't there.

If you are very tired, you will need to balance activity with rest. It's OK to rest when you need to. Sometimes it's really hard for people to allow themselves to rest when they are used to working all day or taking care of a household, but this is not the time to push yourself too hard. Listen to your body and rest when you need to. (For more information

on fatigue and other side effects, please see the Physical Side Effects section of our website or “Additional resources for non-Hodgkin lymphoma” to get a list of available information.

Keep in mind exercise can improve your physical and emotional health.

- It improves your cardiovascular (heart and circulation) fitness.
- Along with a good diet, it will help you get to and stay at a healthy weight.
- It makes your muscles stronger.
- It reduces fatigue and helps you have more energy.
- It can help lower anxiety and depression.
- It can make you feel happier.
- It helps you feel better about yourself.

And long term, we know that getting regular physical activity plays a role in helping to lower the risk of some cancers, as well as having other health benefits.

Can I lower my risk of the lymphoma progressing or coming back?

Most people want to know if there are specific lifestyle changes they can make to reduce their risk of lymphoma progressing or coming back. Unfortunately, for most cancers there’s little solid evidence to guide people. This doesn’t mean that nothing will help – it’s just that for the most part this is an area that hasn’t been well studied. Most studies have looked at lifestyle changes as ways of preventing cancer in the first place, not slowing it down or keeping it from coming back.

At this time, not enough is known about non-Hodgkin lymphoma to say for sure if there are things you can do that will be helpful. Adopting healthy behaviors such as not smoking, eating well, and staying at a healthy weight may help, but no one knows for sure. However, we do know that these types of changes can have positive effects on your health that can extend beyond your risk of lymphoma or other cancers.

How does having non-Hodgkin lymphoma affect your emotional health?

During and after treatment, you may find yourself overcome with many different emotions. This happens to a lot of people.

You may find yourself thinking about death and dying. Or maybe you’re more aware of the effect the cancer has on your family, friends, and career. You may take a new look at your relationship with those around you. Unexpected issues may also cause concern. For instance, as you feel better and have fewer doctor visits, you’ll see your health care team

less often and have more time on your hands. These changes can make some people anxious.

Almost everyone who has been through cancer can benefit from getting some type of support. You need people you can turn to for strength and comfort. Support can come in many forms: family, friends, cancer support groups, church or spiritual groups, online support communities, or one-on-one counselors. What's best for you depends on your situation and personality. Some people feel safe in peer-support groups or education groups. Others would rather talk in an informal setting, such as church. Others may feel more at ease talking one-on-one with a trusted friend or counselor. Whatever your source of strength or comfort, make sure you have a place to go with your concerns.

The cancer journey can feel very lonely. It is not necessary or good for you to try to deal with everything on your own. And your friends and family may feel shut out if you don't include them. Let them in, and let in anyone else who you feel may help. If you aren't sure who can help, call your American Cancer Society at 1-800-227-2345 and we can put you in touch with a group or resource that may work for you. You can also read our document *Distress in People with Cancer* or see the Emotional Side Effects section of our website for more information.

If treatment for non-Hodgkin lymphoma stops working

Non-Hodgkin lymphoma (NHL) is a diverse group of diseases, and the chance of progression or recurrence after treatment varies among types.

In many cases, NHL that comes back after treatment (recurs) will respond to new kinds of chemotherapy or other drugs. If a remission can be achieved with the second round of treatment, doctors often recommend high-dose chemo with a stem cell transplant or a low-dose, non-myeloablative transplant, if possible.

If several rounds of chemo have already been tried, the lymphoma is much less likely to respond to additional or new chemo. If the lymphoma does respond, the response may be shorter. Over time, chemo usually provides less benefit, although immunotherapy and other new approaches to treatment available through clinical trials may be effective.

For general information on dealing with a recurrence, see our document *When Your Cancer Comes Back: Cancer Recurrence*.

At some point, even newer treatments may no longer be effective. If this happens, it's important to weigh the possible limited benefits of any new treatment against the possible downsides. Everyone has their own way of looking at this.

This is likely to be the hardest part of your battle with cancer – when you have been through many medical treatments and nothing's working anymore. Your doctor may offer you new options, but at some point you may need to consider that treatment is not likely to improve your health or change your outcome or survival.

If you want to continue to get treatment for as long as you can, you need to think about the odds of treatment having any benefit and how this compares to the possible risks and side effects. In many cases, your doctor can estimate how likely it is the cancer will respond to treatment you are considering. For instance, the doctor may say that more chemo or radiation might have about a 1 in 100 chance of working. Some people are still tempted to try this. But it's important to think about and understand your reasons for choosing this plan.

No matter what you decide to do, you need to feel as good as you can. Make sure you are asking for and getting treatment for any symptoms you might have, such as nausea or pain. This type of treatment is called *palliative care*.

Palliative care helps relieve symptoms, but is not expected to cure the disease. It can be given along with cancer treatment, or can even be cancer treatment. The difference is its purpose – the main purpose of palliative care is to improve the quality of your life, or help you feel as good as you can for as long as you can. Sometimes this means using drugs to help with symptoms like pain or nausea. Sometimes, though, the treatments used to control your symptoms are the same as those used to treat cancer. For instance, radiation might be used to help relieve bone pain caused by cancer that has spread to the bones. Or chemo might be used to help shrink a tumor and keep it from blocking the bowels. But this is not the same as treatment to try to cure the cancer. You can learn more about physical and emotional changes, as well as plans and preparations for yourself and your family, in our document *Nearing the End of Life*.

At some point, you may benefit from hospice care. This is special care that treats the person rather than the disease; it focuses on quality rather than length of life. Most of the time, it's given at home. Your cancer may be causing problems that need to be managed, and hospice focuses on your comfort. You should know that while getting hospice care often means the end of treatments such as chemo and radiation, it doesn't mean you can't have treatment for the problems caused by the cancer or other health conditions. In hospice the focus of your care is on living life as fully as possible and feeling as well as you can at this difficult time. You can learn more in our document *Hospice Care*.

Staying hopeful is important, too. Your hope for a cure may not be as bright, but there's still hope for good times with family and friends – times that are filled with happiness and meaning. Pausing at this time in your cancer treatment gives you a chance to refocus on the most important things in your life. Now is the time to do some things you've always wanted to do and to stop doing the things you no longer want to do. Though the cancer may be beyond your control, there are still choices you can make.

What's new in non-Hodgkin lymphoma research and treatment?

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

Genetics

Scientists are making a lot of progress in understanding how changes in DNA can cause normal lymphocytes to develop into lymphoma cells. This is providing insight into why these cells may grow too rapidly, live too long, and not develop into mature cells that take part in normal immune reactions. Once this is understood, drugs may be developed that block this process.

Progress in understanding DNA changes in lymphoma has already provided improved and highly sensitive tests for detecting this disease. Such tests can identify lymphoma cells based on changes such as chromosome translocations or rearrangements or specific gene mutations. 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 and if a relapse is likely

Treatment

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

Chemotherapy

Many new chemotherapy drugs are being studied in clinical trials. In recent years, these studies have led to the approval of drugs such as bendamustine (Treanda) and pralatrexate (Folotyn) for use against certain types of lymphoma. Other studies are looking at new ways to combine drugs using different doses or different sequences of drugs.

Bone marrow and peripheral blood stem cell transplants

Researchers continue to improve bone marrow and peripheral blood stem cell transplant methods, including new ways to collect these cells before the transplant.

Autologous transplants (which use stem cells from the patient rather than from another person) have the risk of reintroducing lymphoma cells back into the patient after treatment. Researchers are testing new and improved ways to remove 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.

A lot of research is focusing on eliminating graft-versus-host disease in allogeneic (donor) transplants. This work revolves around altering the transplanted T-cells so that they won't react with the recipient's normal cells but still kill the lymphoma cells.

Researchers are also studying the effectiveness of non-myeloablative (reduced-intensity) stem cell transplants in people with lymphoma. This approach may allow more people to benefit from stem cell transplants.

Targeted therapies

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

Targeted drugs such as bortezomib (Velcade), romidepsin (Istodax), and temsirolimus (Torisel) have shown some promise in treating certain lymphomas. These and similar drugs are now being studied in clinical trials.

Antibiotics

Gastric MALT lymphoma, which is linked to infection by the bacteria *Helicobacter pylori*, can often be treated with antibiotics against that bacterium. MALT lymphoma of the tissues around the eye (called *ocular adnexal marginal zone lymphoma*) has been linked to infection with the bacterium, *Chlamydomphila psittaci*. One study has shown that treating the infection with an antibiotic (doxycycline) can make this lymphoma get better and even go away. More studies may be needed before antibiotics become part of the standard treatment for this type of lymphoma.

Monoclonal antibodies

Lymphoma cells contain certain chemicals on their surface. Monoclonal antibodies that recognize these substances can be targeted to destroy the lymphoma cells while causing little damage to normal body tissues. This treatment strategy has already proven effective. Several such drugs, including rituximab, are already available and are discussed in the section "Immunotherapy for non-Hodgkin lymphoma."

Rituximab is most often given for a limited amount of time during treatment. Because it has few side effects, it's been studied to see if using it long-term will help prevent lymphomas from coming back and help patients live longer. It does seem to help some patients with follicular lymphoma live longer, but using it long term for other lymphomas is still being studied.

Because of the success of rituximab and similar drugs such as ibritumomab and tositumomab, new monoclonal antibodies have been developed. One example is epratuzumab, which targets the CD22 antigen on certain lymphoma cells.

Some newer antibodies are attached to substances that can poison cancer cells, and are known as *immunotoxins*. They act as homing devices to deliver the toxins directly to the cancer cells. One example of this is brentuximab vedotin (Adcetris), which is made up of an antibody to CD30 that is attached to a cell poison. It has been shown to help treat patients with anaplastic large cell lymphoma (ALCL) that is not responding to treatment with chemo.

Another immunotoxin, known as CAT-3888 (BL22), targets the CD22 antigen on certain lymphoma cells, bringing along a toxin known as PE38. This drug showed a great deal of promise in treating hairy cell leukemia (HCL) in early clinical trials. A newer version of this drug, known as CAT-8015 (moxetumomab pasudotox), is now being studied for use against lymphomas.

Lymphoma vaccines

Doctors have known for some time that people's immune systems may help fight their cancer. In rare instances, these people's immune systems have rejected their cancers, and they have been cured. Scientists are now trying to develop ways to encourage this immune reaction by using vaccines.

Unlike vaccines against infections like measles or mumps, these vaccines are designed to help treat, not prevent, lymphomas. The goal is to create an immune reaction against lymphoma cells in patients who have very early disease or in patients whose disease is in remission. One possible advantage of these types of treatments is that they seem to have very limited side effects. So far, there have been a few successes with this approach, and it's a major area of research in lymphoma treatment. At this time lymphoma vaccines are only available in clinical trials.

*BiovaxID*TM is a vaccine based on the unique genetic makeup of a patient's B-cell non-Hodgkin lymphoma. The vaccine uses a unique protein (part of an antibody called an *idiotype*) taken from each patient's own lymphoma cells, which are obtained during a biopsy. This protein is combined with substances that boost the body's immune response when the combination is injected into the patient. A late-stage clinical trial found that in people with follicular lymphomas that went away after chemotherapy, the vaccine lengthened the time before the lymphoma came back by more than a year. The vaccine has also shown promising early results against mantle cell lymphoma. It is not yet available outside of clinical trials.

Additional resources for non-Hodgkin lymphoma

More information from your American Cancer Society

Here is more information you might find helpful. You can order free copies of our documents from our toll-free number, 1-800-227-2345, or read them on our website.

Living with cancer

Health Professionals Associated With Cancer Care

Talking With Your Doctor (also in Spanish)

After Diagnosis: A Guide for Patients and Families (also in Spanish)

Nutrition for the Person With Cancer During Treatment: A Guide for Patients and Families (also in Spanish)

Coping With Cancer in Everyday Life (also in Spanish)

Cancer treatments

A Guide to Cancer Surgery (also in Spanish)

A Guide to Chemotherapy (also in Spanish)

Understanding Radiation Therapy: A Guide for Patients and Families (also in Spanish)

Targeted Therapy

Immunotherapy

Clinical Trials: What You Need to Know

Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants)

Cancer treatment side effects

Caring for the Patient With Cancer at Home: A Guide for Patients and Families (also in Spanish)

Distress in People With Cancer

Anxiety, Fear, and Depression

Nausea and Vomiting

Guide to Controlling Cancer Pain (also in Spanish)

Get Relief From Cancer Pain

Pain Diary

Anemia in People With Cancer

Fatigue in People With Cancer

Family and caregiver concerns

Talking With Friends and Relatives About Your Cancer (also in Spanish)

Helping Children When A Family Member Has Cancer: Dealing With Diagnosis (also in Spanish)

What It Takes to Be a Caregiver

Insurance and financial issues

In Treatment: Financial Guidance for Cancer Survivors and Their Families (also in Spanish)

Health Insurance and Financial Assistance for the Cancer Patient (also in Spanish)

Your American Cancer Society also has books that you might find helpful. Call us at 1-800-227-2345 or visit our bookstore online at cancer.org/bookstore to find out about costs or to place an order.

National organizations and websites*

Along with the American Cancer Society, other sources of information and support include:

Lymphoma

Leukemia & Lymphoma Society

Toll-free number: 1-800-955-4572

Website: www.lls.org

Has a variety of service programs and resources available throughout the US and Canada including: the Information Resource Center, staffed by healthcare professionals, available via the toll-free number; free publications on all forms of lymphoma and related topics; First Connection, a telephone-based peer support network for patients and survivors; family support groups; education teleconferences and web-casts – a schedule is on the website.

Lymphoma Research Foundation

Toll-free number: 1-800-500-9976

Website: www.lymphoma.org

Provides a help line for information on lymphoma and its treatment; educational materials; clinical trial information; peer support programs/support groups; financial aid for treatment-related expenses, when available; quarterly newsletters; and national/regional/local educational conferences for the public.

National Cancer Institute (NCI)

Toll-free number: 1-800-422-6237 (1-800-4-CANCER)

TTY: 1-800-332-8615

Website: www.cancer.gov

Their “Cancer Information Service” offers a wide variety of free, accurate, up-to-date information about cancer to patients, their families, and the general public; also can help people find clinical trials in their area.

National Coalition for Cancer Survivorship (NCCS)

Toll-free number: 1-888-650-9127

Website: www.canceradvocacy.org

Has publications on many cancer-related topics; also offers the Cancer Survival Toolbox – a free program that teaches skills that can help people with cancer meet the challenges of their illness.

Bone marrow and peripheral blood stem cell transplants

National Bone Marrow Transplant Link (nbmtLINK)

Toll-free number: 1-800-546-5268 (1-800-LINK-BMT)

Website: www.nbmtlink.org

Programs and services include: information and referrals to meet a wide range of needs; support via one-on-one conversations with trained peer support volunteers who are transplant survivors, caregivers, and donors; telephone support groups, facilitated by a clinical social worker, that link patients and families together to offer mutual support and coping strategies; and the nbmtLINK Online Resource Library – a comprehensive, searchable library giving access to the latest transplant information.

Be the Match (formerly the National Marrow Donor Program)

Toll-free number: 1-800-627-7692 (1-800-MARROW-2)

Website: www.bethematch.org

Provides a registry of volunteer bone marrow donors and cord blood units (the largest listing in the world), as well as a searchable listing of transplant centers that can be accessed directly at www.marrow.org/access. This listing contains information that may help a patient choose a transplant center. Also supports patients and their doctors throughout the transplant process, from diagnosis through survivorship; matches patients with the best donor or cord blood unit using innovative science and technology; has free educational materials; and offers financial assistance to eligible underinsured patients through the Patient Assistance Program.

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

No matter who you are, we can help. Contact us anytime, day or night, for information and support. Call us at **1-800-227-2345** or visit www.cancer.org.

References: Non-Hodgkin lymphoma detailed guide

American Cancer Society. *Cancer Facts & Figures 2015*. Atlanta, Ga: American Cancer Society; 2015.

Dunleavy K, Wilson WH. Diagnosis and treatment of non-Hodgkin lymphoma (aggressive). In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P, eds. *Hematology: Basic Principles and Practice*. 5th ed. Philadelphia, Pa: Elsevier; 2009:1293-1302.

Evens AM, Winter JN, Gordon LI, et al. Non-Hodgkin lymphoma. In: Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ, eds. *Cancer Management: A Multidisciplinary Approach*. 13th ed. Lawrence, KS: UBM Medica; 2010:739-794.

Ferreri AJ, Govi S, Pasini E, et al. Chlamydomyces psittaci eradication with doxycycline as first-line targeted therapy for ocular adnexae lymphoma: final results of an international phase II trial. *J Clin Oncol*. 2012;30(24):2988-2994.

Friedberg JW, Mauch PM, Rimsza LM, Fisher RI. Non-Hodgkin lymphomas. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2011:1855-1893.

Gribben JG. Clinical manifestations, staging, and treatment of indolent non-Hodgkin's lymphoma. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P, eds. *Hematology: Basic Principles and Practice*. 5th ed. Philadelphia, Pa: Elsevier; 2009:1281-1292.

Hartge P, Smith MT. Environmental and behavioral factors and the risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev*. 2007;16:367-368.

Hawkes EA, Wotherspoon A, Cunningham D. Diagnosis and management of rare gastrointestinal lymphomas. *Leuk Lymphoma*. 2012 Dec;53(12):2341-2350. Epub 2012 Jun 21.

Howlader N, Noone AM, Krapcho M (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.

Jaffe ES, Pittaluga S. The pathologic basis for the classification of non-Hodgkin's lymphoma. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P, eds. *Hematology: Basic Principles and Practice*. 5th ed. Philadelphia, Pa: Elsevier; 2009:1265-1280.

Kreitman RJ, Stetler-Stevenson M, Margulies I, et al. Phase II trial of recombinant immunotoxin RFB4(dsFv)-PE38 (BL22) in patients with hairy cell leukemia. *J Clin Oncol*. 2009;27:2983-2990.

Micallef IN, Maurer MJ, Wiseman GA, et al. Epratuzumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy in patients with previously untreated diffuse large B-cell lymphoma. *Blood*. 2011;118(15):4053-4061.

Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States 1992-2001. *Blood*. 2006;107:265-276.

National Cancer Institute. Physician Data Query (PDQ). Adult Non-Hodgkin Lymphoma Treatment. 4/11/2014. Accessed at www.cancer.gov/cancertopics/pdq/treatment/adult-non-hodgkins/healthprofessional on June 27, 2014.

National Comprehensive Cancer Network (NCCN). Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas. Version 2.2014. Accessed at www.nccn.org on June 30, 2014.

Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196. Epub 2012 May 21.

Rizvi MA, Evens AM, Tallman MS, et al. T-cell non-Hodgkin lymphoma. *Blood*. 2006;107:1255-1264.

Schuster SJ, Neelapu SS, Gause BL, et al. Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma. *J Clin Oncol*. 2011;29(20):2787-2794.

Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 2007;109:1857-1861.

Solal-Celigny P, Roy P, Colombat P, et al. Follicular Lymphoma International Prognostic Index. *Blood*. 2004;104:1258-1265.

Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013 Aug 8;369(6):507-16. Epub 2013 Jun 19.

Roschewski MJ, Wilson WH. Non-Hodgkin's Lymphoma. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, Pa: Elsevier; 2014:2033-2059.

Vidal L, Gafter-Gvili A, Leibovici L, Shpilberg O. Rituximab as maintenance therapy for patients with follicular lymphoma. *Cochrane Database Syst Rev*. 2009;(2):CD006552.

Last Medical Review: 8/26/2014

Last Revised: 1/28/2015

2014 Copyright American Cancer Society

For additional assistance please contact your American Cancer Society
1-800-227-2345 or www.cancer.org