**Oncology Part Three**

**T-Cell Prolymphocytic Leukemia**

In individuals with T-PLL, mutations in T-cell genes disrupt typical cell maturation, leading to uncontrolled growth and division. This causes cancerous cells to multiply rapidly and spread throughout the body, crowding out healthy cells.

This rare form of leukemia accounts for approximately 2% of adult mature lymphocytic leukemias. It most often affects people older than 65 years, although it can affect individuals in their 30s to 90s.

T-PLL is a rare and aggressive type of blood cancer that affects T cells, a type of white blood cell. These cells are part of the immune system that helps fight infection.

In people with T-PLL, changes or mutations in T-cell genes disrupt typical cell maturation and cause the cells to grow uncontrollably and rapidly. The number of immature, nonfunctional T cells increase, making it difficult for the body to produce new, healthy blood cells.

## **Signs and symptoms**

As a result of these cellular changes, a person develops various signs and symptoms. Common signs of T-PLL include:

* swollen lymph nodes
* enlarged liver and spleen
* night sweats
* weight loss
* fatigue
* weakness
* skin lesions or rashes
* high white blood cell counts
* low red blood cell counts, or anemia
* low platelet counts

## **Causes**

Doctors do not know the exact cause of T-PLL. However, it appears to involve certain mutations in T-cell genes that trigger typical T-cells to become leukemia cells.

The most common DNA changes are in proto-oncogene TCL-1, a cell growth and division gene. The genetic mutations turn it into an oncogene, which can trigger the growth of cancer cells.

Certain people, such as males and those over 65 years, are more likely to develop T-PLL. However, unlike other cancers, no known environmental risk factors exist.

## **Survival rate**

T-PLL is aggressive, and the outlook is generally unfavorable.

The overall survival rate for T-PLL varies depending on several factors, including the individual’s age, general health status, and the extent of the genetic abnormalities.

The survival time for individuals with T-PLL is typically less than 2 years from diagnosis, although some individuals may survive longer with appropriate treatment.

## **Diagnosis and test**

Diagnosing T-PLL is complicated and typically involves several steps to confirm the presence of the disease and determine its extent. The initial evaluation often includes a physical examination and blood tests.

These tests assess the levels of blood cells, including T lymphocytes, and look for signs of anemia or other abnormalities.

Doctors may use the following tests to diagnose PLL:

* Bone marrow biopsy: This checks if the bone marrow is healthy or making atypical cells.
* Peripheral blood smears: These check for T-cell changes.
* Immunophenotyping: This looks for markers on the surface of leukemia cells.
* Chromosome analysis: This checks to see if there are genetic changes.
* Imaging studies: These assess the extent of the disease.

## **Treatment**

T-PLL treatment involves a combination of therapies to control and manage the disease’s symptoms. The specific treatment approach depends on several factors, including the individual’s age, overall health status, and the extent of the disease.

Current treatment approaches include:

* Watching and waiting: Around 10–15% of those with T-PLL do not have symptoms during diagnosis. Therefore, doctors may delay treatment and monitor the individual to check for disease progression.
* Medications: For people with symptomatic T-PLL, drugs, including intravenous alemtuzumab (Campath) and alemtuzumab plus pentostatin (Nipent), may help control the disease.
* Hematopoietic stem cell transplantation: Doctors may suggest a stem cell transplant in people who achieve disease remission following drug therapy. This is the only treatment that may offer a potential cure.

People with T-PLL should explore all available treatment options, including participating in clinical trials. These offer access to new and innovative therapies that can help improve outcomes for individuals with this disease.

Clinical trials may involve testing new drugs, drug combinations, or dosing schedules, allowing people to benefit from new therapies that may not yet be widely available.

## **Contacting a doctor**

T-PLL is an aggressive cancer that requires timely diagnosis and treatment.

If someone experiences symptoms relating to T-PLL, they should contact their doctor immediately for evaluation. Early diagnosis and treatment can help improve outcomes for those with the disease.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of T-PLL includes other lymphoid neoplasms with a leukemic presentation; some relevant entities include :

* B cell prolymphocytic leukemia (B-PLL); B-PLL, compared to T-PLL, has minimal lymphadenopathy and rarely involves skin involvement. It shows a strong B-cell marker study (CD19, CD20, CD22) with additional positive markers of CD79a and CD5. CD23 is negative. The cytogenetics shows no t(11;14), but there is positivity for 13q del, 11q del, 17p del, or 6q del. The median survival in B-PLL is 3 years, measured in months for T-PLL. Cytologically, they bear a single prominent nucleolus.
* Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL): The cells are variably positive for CD5 and CD23 and weakly positive for CD22 and CD79b. They are CD10 negative. The cytogenetic analysis shows 13q del, 11q del, 17p del, or trisomy 12.
* Mycosis fungoides (MF) / Sezary syndrome (SS): Cells in Sezary syndrome are positive for CD2 and CD3. They are predominantly positive for CD4. They are positive for CD25 and negative for TCL1. They are usually negative for CD7 and CD26. Skin lesions may be found in as many as 20% of patients. A skin biopsy may be needed to exclude Sezary syndrome. The rash in SS is felt to be the harbinger of its lymphocytosis.
* Adult T cell lymphoma/leukemia (ATLL): Chronic HTLV-1 infection is thought to be the etiology of this neoplasm. HTLV-1 PCR/serology is positive; T-PLL cells are negative for this indication. ATLL cells are TCL1 negative. They are positive for CD3, CD4, and CD25. They are CD7 negative; T-PLL cells are CD7 positive. By far, in ATLL, CD4 is more prevalent than CD8. Hypercalcemia is common in ATLL but NOT found in T-PLL. ATLL cells have a unique cytomorphology with "flower cells." These are cells having convoluted nuclei with condensed, homogeneous chromatin.
* T cell large granular lymphocyte leukemia (LGL): These cells are TCL1 negative but positive for CD2, CD3, CD8, CD16, and CD57. They variably express CD7 and rarely CD4. The patients may have mild-to-moderate splenomegaly but rarely lymphadenopathy. Cytopenias are a frequent finding. The cytology reveals large lymphocytes containing azurophilic granules. The median survival is over 10 years.
* Hairy cell leukemia (HCL); HCL is rare and is noted to be a low-grade mature B-cell cancer. 'Classic' HCL bears B-cell markers of CD19, CD20, and CD22. Markers more specific for this entity include CD11c, CD25, CD103, CD125, and CD200. An HCL variant exists that is missing both CD25 and CD123. CD22 and CD79b are variably expressed. However, the variant contains a characteristic BRAF-V600E mutation, a marker not evident in other B-cell maladies. The physical exam is noteworthy for massive splenomegaly, essentially its most prominent feature. Cellular morphology shows "hair"-like cytoplasmic projections. The variant form may manifest nucleoli.

**PROGNOSIS**

T-PLL is an aggressive malignancy with a median survival of 1 to 2 years. The median overall survival is 21 months. Some patients may present with the indolent variant, which shows a better prognosis. Poor prognostic factors include age above 65, effusion, hepatic or nervous system involvement, bulky lymph nodes, high absolute lymphocytic count, high expression of TCL1 and AKT1, and JAK3 mutation. Having at least 5 cytogenetic abnormalities was a negative prognostic factor for survival. An elevated LDH or beta-2-microglobulin reportedly portends a poor response to therapy.

**EPIDEMIOLOGY**

T-PLL is a rare T-cell leukemia. It accounts for approximately 2% of mature lymphocytic leukemia cases in adults. The pathology is common in elderly patients (older than 65 years) aged 30 to 94. There is a slight male predominance, with a male-to-female ratio of 1.33.

REFERENCE

<https://www.ncbi.nlm.nih.gov/books/NBK541000/#article-50561.s9>

### **Large granular lymphocytic leukemia (LGL)**

**DEFINITION AND DESCRIPTION**

Large granular lymphocytic leukemia (LGL) is a rare type of chronic leukemia that affects specific white blood cells known as lymphocytes. Lymphocytes fight viruses and make antibodies that help fight infection.

There are two types of large granular lymphocytic leukemia: T-cell large granular lymphocytic leukemia (T-LGL) and chronic lymphoproliferative disorder of NK cells (CLPD-NK). These conditions start in white blood cells called cytotoxic T cells or natural killer cells. Both types of large granular lymphocytic leukemia grow slowly. They typically affect people age 60 and older. Healthcare providers can treat LGL, but the condition sometimes comes back and can become a chronic health issue.

#### **How does this condition affect my body?**

LGL is a type of chronic lymphocytic leukemia that occurs when certain T cells and natural killer cells mutate, becoming abnormal cells that keep your bone marrow from producing normal blood cells. People with LGL often develop neutropenia, meaning they produce low numbers of granulocytes (the most common white blood cells) and have an increased risk of infection. They may also develop anemia, which happens because LGL cells affect red blood cell production.

## **Symptoms**

People may have this condition and never have symptoms. One study showed about one-third of people with LGL didn’t have any symptoms when they were diagnosed. Instead, they learned they had LGL because blood tests showed they had unusually low red blood levels or low levels of neutrophils (a type of granulocyte). In some cases, people are diagnosed with LGL because they’re being treated for blood disorders and they have symptoms that healthcare providers link to large granular lymphocytic leukemia.

People with LGL who do have symptoms often have the following:

* Fatigue: Extreme tiredness is the most common LGL symptom and is likely due to anemia.
* Frequent fevers and recurring infections: People have fevers caused by bacterial infections.
* Enlarged spleen (splenomegaly): Infections and some types of anemia may cause your spleen to become enlarged.

#### **What conditions are linked to large granular lymphocytic leukemia?**

Many people with LGL have autoimmune diseases, particularly rheumatoid arthritis. Other common conditions are:

* Anemia: This condition means you don’t have enough healthy red blood cells and hemoglobin. Many times, people have severe anemia and rely on blood transfusions to maintain red blood cell levels. Some people with LGL have hemolytic anemia, which happens because red blood cells are destroyed and not because of low red blood cell production.
* Lymphocytosis: This is having a high lymphocyte (white blood cell) count. People who have lymphocytic leukemias or lymphomas and viral infections usually have low lymphocyte counts.

### **causes of large granular lymphocytic leukemia**

Healthcare providers aren’t sure what causes the condition, but they believe there’s a link between this type of leukemia and immune responses, autoimmune diseases or other cancers:

* About 30% of people with this condition also have rheumatoid arthritis and other autoimmune diseases.
* Another 25% to 30% have another kind of lymphoma or other kinds of cancer.
* Many people with this condition also carry mutated forms of two genes — *STAT3* and *STAT5B* — that play roles in cell immunity and how cells divide and multiply.

## **Diagnosis and Tests**

Healthcare providers typically do blood tests and genetic analyses to diagnose this condition. Common tests may include:

* Complete blood count (CBC) with differential: A CBC with differential is a measure of all of your blood cells, including the number of each type of white blood cell.
* Peripheral blood smear: This is a technique healthcare providers use to examine blood cells under a microscope so they can count the number of LGLs in your blood.
* Flow cytometry: This lab test analyzes cell characteristics. Healthcare providers often use this test to diagnose and classify types of leukemia.
* Immunophenotyping: Healthcare providers analyze blood or tissue samples for signs of markers on cell surfaces. Markers indicate specific types of certain conditions.
* T-cell receptor (TCR) gene rearrangement analysis: Healthcare providers use these blood or bone marrow tests to look for problems in the genes that control how your T-cells work.
* Genetic testing: Healthcare providers may test for *STAT3* and *STAT5* gene mutations.

They may do other tests, including bone marrow examinations, to rule out conditions including immunodeficiency, rheumatoid arthritis, myelodysplasia and myeloid mutations. They may also check immunoglobulin levels and monoclonal protein levels.

## **Management and Treatment**

If you have T-LGL or CLPD-NK leukemia but don’t have symptoms, your provider may recommend watchful waiting. In watchful waiting, providers monitor your health, typically taking blood tests every few months and watching for signs of symptoms.

People who do have symptoms may receive immunosuppressive therapy and steroids. Healthcare providers may use one treatment after another or use low-intensity forms of treatment. Because LGL is a rare condition, people often seek out doctors who specialize in this disease.

## **Outlook / Prognosis**

Most of the time, large granular lymphocytic leukemia is a chronic illness that isn’t fatal. About 75% of people with T-LGL leukemia and CLPD-LGL leukemia are alive five years after diagnosis. About 10% of people with these types of leukemia die of severe infections that are complications of leukemia.

## **Prevention**

No, you can’t. Healthcare providers don’t know the exact cause of large lymphocytic granular leukemia, so they can’t say how you might avoid it. That said, people who have autoimmune diseases have an increased risk of developing this condition. If you have an autoimmune disease, ask your healthcare provider whether you should be concerned about developing LGL.

## **Living With**

If you have a type of large granular lymphocytic leukemia, you may not have symptoms but you should take steps like monitoring your overall health and having regular checkups. Regardless of whether you have symptoms, the following suggestions may be helpful:

* Eat a healthy diet of lean protein, fruits, vegetables and whole grains.
* Exercise regularly.
* Get enough rest.
* Manage your stress.
* Protect your immune system: Ask your provider about vaccinations and other things you should do to avoid infection.

### **Can you live a normal life with this condition?**

In general, people treated for LGL can typically live normal lives and have the same lifespan as people who don’t have the condition. It’s important to remember that some people who have LGL already have serious blood disorders that affect their quality of life.

### **When should I see my healthcare provider?**

You should see your healthcare provider if you develop symptoms that may be signs your condition is getting worse. If you have symptoms and are receiving treatment, you should see your provider if you notice changes in your body, such as symptoms that are getting worse.

### **Differential Diagnosis**

#### **Reactive LGL proliferation.**

Many conditions can lead to the development of reactive LGL proliferation, including splenectomy, solid organ or bone marrow graft, viral infections (human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus), solid tumor, and non-Hodgkin lymphoma. LGL proliferations are typically poly- or oligoclonal, last only several months, and are not responsible for cytopenias. In difficult cases, bone marrow biopsy could help because in reactive LGL proliferation, bone marrow infiltration is absent.

#### **Bone marrow failure syndromes.**

Bone marrow failure syndromes (aplastic anemia, paroxysmal nocturnal hemoglobinuria, and myelodysplastic syndrome [MDS]) are occasionally associated with LGL leukemia. STAT3 mutation was found in few patients with aplastic anemia and MDS with concomitant LGL leukemia, suggesting similar pathogenesis. In this series, STAT-3-mutated patients with aplastic anemia were more sensitive to immunosuppressive therapies, and STAT-3-mutated patients with MDS harbored a lower degree of bone marrow cellularity. Efficacy of immunosuppressive treatments directed against T lymphocyte–mediated immune response is a strong argument for a common role of autoreactive T cells in all of these diseases. Moreover, concurrent STAT3, DNMT3A, and TET2 mutations were found in a patient with T-LGL without MDS morphologic abnormalities, and those mutations were restricted to CD3+ T cells. The two latter mutations are recurrent mutations usually found in MDS.

A recent study revealed several cases of unexplained cytopenia in which STAT3 mutation status could after all correct the diagnosis. Those cases were classified as MDS without typical bone marrow dysplasia nor MDS typical mutation using next-generation sequencing analysis. This review suggests that it could be useful to add the Stat3 SH2 domain to the myeloid next-generation sequencing panel.

**EPIDEMIOLOGY**

LGL leukemia is a rare disorder constituting 2-5% of all chronic lymphoproliferative diseases in the US and Europe and 5-6% of all cases in the Asian population . Recent demographic studies of European and North American cohorts place the average incidence of LGL leukemia at 0.2-0.72 per million persons per year.

The incidence is approximately the same in both males and females. The median age at presentation is the middle age group (55-60 years) and it is less common in pediatric age groups. The aggressive variant is more common in the Asian continent. Females are diagnosed at a younger age compared with males. In a US-based population study, 14% of patients were under the age of 50 years at the time of diagnosis, in contrast to another French registry database that reported 26% patients <50 years of age.

The affiliation of LGL leukemia with autoimmune diseases creates a hindrance in the interpretation of the actual incidence of this leukemia as many patients have already received steroids and/or immunosuppressive therapies for the primary autoimmune diseases diagnosed before, concurrently, or after the diagnosis of the LGL leukemia. Nevertheless, certain ethnicities notably Asians of Japanese, Koreans, and Taiwanese descent have established predilection towards the form of Aggressive NK cell-leukemia. No definite sex predilection is found within these ethnic populations. However, the age group affected is younger, earlier by a decade or two from the other spectrum of LGL leukemia.

REFERENCE

[Large granular lymphocytic leukemia: a brief review - PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC8918699/#sec2)

[Large Granular Lymphocytic Leukemia: Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/24128-large-granular-lymphocytic-leukemia)

### **Leukemia**

**Definition and description**

Leukemia is a cancer of the blood and bone marrow marked by excessive production of abnormal white blood cells that fail to fight infections and crowd out normal blood cells

Leukemia is cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system.

Many types of leukemia exist. Some forms of leukemia are more common in children. Other forms of leukemia occur mostly in adults.

Leukemia usually involves the white blood cells. Your white blood cells are potent infection fighters — they normally grow and divide in an orderly way, as your body needs them. But in people with leukemia, the bone marrow produces an excessive amount of abnormal white blood cells, which don't function properly.

Treatment for leukemia can be complex — depending on the type of leukemia and other factors. But there are strategies and resources that can help make your treatment successful.

**leukemia**, a cancer of the blood-forming tissues characterized by a large increase in the numbers of white blood cells (leukocytes) in the circulation or bone marrow. A number of different leukemias are classified according to the course of the disease and the predominant type of white blood cell involved. Some types of leukemia have been related to radiation exposure, as noted in the Japanese population exposed to the first atomic bomb at Hiroshima; other evidence suggests hereditary susceptibility.

Leukemias are defined as either acute or chronic and as either myelogenous (from bone marrow) or lymphocytic (involving lymphocytes). These characteristics are used to designate almost all cases as one of four types—acute myelogenous, acute lymphocytic, chronic myelogenous, and chronic lymphocytic leukemia. Acute leukemias affect immature cells; the disease develops rapidly, with symptoms including anemia, fever, bleeding, and swelling of the lymph nodes. Immature leukemia cells continue to divide in the bone marrow, which leads to rapid death if left untreated. In chronic leukemia the cells develop and are transported to the tissues, but the cells do not function normally. Myelogenous leukemia affects granulocytes and monocytes, white blood cells that destroy bacteria and some parasites.

The most common form in children, acute lymphocytic leukemia, once killed more than 90 percent of its victims within six months. With new drug therapies, the majority of acute lymphocytic patients now achieve complete remission, with no evidence of malignant cells in the blood. With continued therapy, more than half remain free of disease for five years or longer. These patients are presumed to be cured.

The disease is characterized by the uncontrolled growth of blood cells, usually white blood cells in the bone marrow. White blood cells are a fundamental component of the body’s immune response. Leukemia cells crowd out and replace normal blood and marrow cells.

The exact cause of leukemia isn’t known, but researchers believe the disease develops due to mutations in the DNA of certain blood cells, caused by other genetic or environmental factors.

Although many types of leukemia exist, some affect adults more commonly than others.

**Symptoms of leukemia**

Leukemia symptoms vary, depending on the type of leukemia. Common leukemia signs and symptoms include:

* Fever or chills
* Persistent fatigue, weakness
* Frequent or severe infections
* Losing weight without trying
* Swollen lymph nodes, enlarged liver or spleen
* Easy bleeding or bruising
* Recurrent nosebleeds
* Tiny red spots in your skin (petechiae)
* Excessive sweating, especially at night
* Bone pain or tenderness

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### **When to see a doctor**

Make an appointment with your doctor if you have any persistent signs or symptoms that worry you.

Leukemia symptoms are often vague and not specific. You may overlook early leukemia symptoms because they may resemble symptoms of the flu and other common illnesses.

Sometimes leukemia is discovered during blood tests for some other condition.

Scientists don't understand the exact causes of leukemia. It seems to develop from a combination of genetic and environmental factors.

### **How leukemia forms**

In general, leukemia is thought to occur when some blood cells acquire changes (mutations) in their genetic material or DNA. A cell's DNA contains the instructions that tell a cell what to do. Normally, the DNA tells the cell to grow at a set rate and to die at a set time. In leukemia, the mutations tell the blood cells to continue growing and dividing.

When this happens, blood cell production becomes out of control. Over time, these abnormal cells can crowd out healthy blood cells in the bone marrow, leading to fewer healthy white blood cells, red blood cells and platelets, causing the signs and symptoms of leukemia.

### **How leukemia is classified**

Doctors classify leukemia based on its speed of progression and the type of cells involved.

The first type of classification is by how fast the leukemia progresses:

* **Acute leukemia.** In acute leukemia, the abnormal blood cells are immature blood cells (blasts). They can't carry out their normal functions, and they multiply rapidly, so the disease worsens quickly. Acute leukemia requires aggressive, timely treatment.
* **Chronic leukemia.** There are many types of chronic leukemias. Some produce too many cells and some cause too few cells to be produced. Chronic leukemia involves more-mature blood cells. These blood cells replicate or accumulate more slowly and can function normally for a period of time. Some forms of chronic leukemia initially produce no early symptoms and can go unnoticed or undiagnosed for years.

The second type of classification is by type of white blood cell affected:

* **Lymphocytic leukemia.** This type of leukemia affects the lymphoid cells (lymphocytes), which form lymphoid or lymphatic tissue. Lymphatic tissue makes up your immune system.
* **Myelogenous (my-uh-LOJ-uh-nus) leukemia.** This type of leukemia affects the myeloid cells. Myeloid cells give rise to red blood cells, white blood cells and platelet-producing cells.

### **Types of leukemia**

The major types of leukemia are:

* **Acute lymphocytic leukemia (ALL).** This is the most common type of leukemia in young children. ALL can also occur in adults.
* **Acute myelogenous leukemia (AML).** AML is a common type of leukemia. It occurs in children and adults. AML is the most common type of acute leukemia in adults.
* **Chronic lymphocytic leukemia (CLL).** With CLL, the most common chronic adult leukemia, you may feel well for years without needing treatment.
* **Chronic myelogenous leukemia (CML).** This type of leukemia mainly affects adults. A person with CML may have few or no symptoms for months or years before entering a phase in which the leukemia cells grow more quickly.
* **Other types.** Other, rarer types of leukemia exist, including hairy cell leukemia, myelodysplastic syndromes and myeloproliferative disorders.

## **Risk factors**

Factors that may increase your risk of developing some types of leukemia include:

* Previous cancer treatment. People who've had certain types of chemotherapy and radiation therapy for other cancers have an increased risk of developing certain types of leukemia.
* Genetic disorders. Genetic abnormalities seem to play a role in the development of leukemia. Certain genetic disorders, such as Down syndrome, are associated with an increased risk of leukemia.
* Exposure to certain chemicals. Exposure to certain chemicals, such as benzene — which is found in gasoline and is used by the chemical industry — is linked to an increased risk of some kinds of leukemia.
* Smoking. Smoking cigarettes increases the risk of acute myelogenous leukemia.
* Family history of leukemia. If members of your family have been diagnosed with leukemia, your risk of the disease may be increased.

However, most people with known risk factors don't get leukemia. And many people with leukemia have none of these risk factors.

### Most forms of leukemia develop when immature white blood cells, red blood cells or platelets grow out of control, taking up space where healthy blood cells should exist. The disease develops when genetic mutations or damage occur in bone marrow tissue, which is responsible for making blood cells. There are four main types of leukemia:

* Acute lymphocytic leukemia (ALL) affects a type of white blood cell called lymphocytes
* Acute myeloid leukemia (AML) affects red blood cells, platelets and a type of white blood cell called myeloblasts
* Chronic lymphocytic leukemia (CLL) affects lymphocytes
* Chronic myeloid leukemia (CML) affects a type of white blood cell called granulocytes

Certain inheritable genetic syndromes also appear to raise risk for AML, although having one doesn’t mean you will develop leukemia. These include:

* Fanconi anemia
* Bloom syndrome
* Ataxia-telangiectasia
* Diamond-Blackfan anemia
* Shwachman-Diamond syndrome
* Li-Fraumeni syndrome
* Neurofibromatosis
* Kostmann syndrome

### **Leukemia Prevention Tips**

Because we don’t know exactly what causes leukemia, the National Cancer Institute doesn’t make specific suggestions on how to prevent it. However, it’s always a good idea to take steps to lower your overall risk of cancer through lifestyle modification. The following guidelines may be useful for leukemia prevention:

* Not using any tobacco products
* Not drinking alcohol
* Maintaining a body mass index below 25
* Being physically active every day
* Eating a diet rich in fruits and vegetables and low in processed meats

### Recommendations for Preventing Leukemia

While there’s no reliable way to prevent cholangiocarcinoma, the following bile duct cancer prevention recommendations may help you reduce your risk for developing the disease:

* Get vaccinated against hepatitis B and take steps to prevent infection with hepatitis C
* Limit alcohol use
* Don’t smoke
* Maintain a body mass index below 25
* Be physically active every day
* Eat a diet rich in fruits and vegetables and limit red and processed meat

**Diagnosis**

Doctors may find chronic leukemia in a routine blood test, before symptoms begin. If this happens, or if you have signs or symptoms that suggest leukemia, you may undergo the following diagnostic exams:

* **Physical exam.** Your doctor will look for physical signs of leukemia, such as pale skin from anemia, swelling of your lymph nodes, and enlargement of your liver and spleen.
* **Blood tests.** By looking at a sample of your blood, your doctor can determine if you have abnormal levels of red or white blood cells or platelets — which may suggest leukemia. A blood test may also show the presence of leukemia cells, though not all types of leukemia cause the leukemia cells to circulate in the blood. Sometimes the leukemia cells stay in the bone marrow.
* **Bone marrow test.** Your doctor may recommend a procedure to remove a sample of bone marrow from your hip bone. The bone marrow is removed using a long, thin needle. The sample is sent to a laboratory to look for leukemia cells. Specialized tests of your leukemia cells may reveal certain characteristics that are used to determine your treatment options.

**Treatment**

Treatment for your leukemia depends on many factors. Your doctor determines your leukemia treatment options based on your age and overall health, the type of leukemia you have, and whether it has spread to other parts of your body, including the central nervous system.

Common treatments used to fight leukemia include:

* **Chemotherapy.** Chemotherapy is the major form of treatment for leukemia. This drug treatment uses chemicals to kill leukemia cells.  
  Depending on the type of leukemia you have, you may receive a single drug or a combination of drugs. These drugs may come in a pill form, or they may be injected directly into a vein.
* **Targeted therapy.** Targeted drug treatments focus on specific abnormalities present within cancer cells. By blocking these abnormalities, targeted drug treatments can cause cancer cells to die. Your leukemia cells will be tested to see if targeted therapy may be helpful for you.
* **Radiation therapy.** Radiation therapy uses X-rays or other high-energy beams to damage leukemia cells and stop their growth. During radiation therapy, you lie on a table while a large machine moves around you, directing the radiation to precise points on your body.  
  You may receive radiation in one specific area of your body where there is a collection of leukemia cells, or you may receive radiation over your whole body. Radiation therapy may be used to prepare for a bone marrow transplant.
* **Bone marrow transplant.** A bone marrow transplant, also called a stem cell transplant, helps reestablish healthy stem cells by replacing unhealthy bone marrow with leukemia-free stem cells that will regenerate healthy bone marrow.  
  Prior to a bone marrow transplant, you receive very high doses of chemotherapy or radiation therapy to destroy your leukemia-producing bone marrow. Then you receive an infusion of blood-forming stem cells that help rebuild your bone marrow.  
  You may receive stem cells from a donor or you may be able to use your own stem cells.
* **Immunotherapy.** Immunotherapy uses your immune system to fight cancer. Your body's disease-fighting immune system may not attack your cancer because the cancer cells produce proteins that help them hide from the immune system cells. Immunotherapy works by interfering with that process.
* **Engineering immune cells to fight leukemia.** A specialized treatment called chimeric antigen receptor (CAR)-T cell therapy takes your body's germ-fighting T cells, engineers them to fight cancer and infuses them back into your body. CAR-T cell therapy might be an option for certain types of leukemia.
* **Clinical trials.** Clinical trials are experiments to test new cancer treatments and new ways of using existing treatments. While clinical trials give you or your child a chance to try the latest cancer treatment, treatment benefits and risks may be uncertain. Discuss the benefits and risks of clinical trials with your doctor.

**Differential diagnosis**

* Acute myeloid leukemia
* Chronic myelomonocytic leukemia
* Chronic neutrophilic leukemia
* Thrombocythemia
* Leukemoid reactions from infections (chronic granulomatous [eg, tuberculosis])
* Tumor necrosis
* Acute Lymphoblastic Leukemia (ALL)
* Anemia
* Aplastic Anemia
* B-Cell Lymphoma
* Bone Marrow Failure
* Chronic Myelogenous Leukemia (CML)
* Lymphoblastic Lymphoma

## **COMPLICATION**

## **Weakened immune system**

Having a weakened immune system is a common complication of AML.

Even if your blood is restored to normal working order with treatment, many of the medicines that are used to treat AML can temporarily weaken your immune system.

This means you're more vulnerable to developing an infection, and any infection you develop could be more serious than usual.

Complications arising from infection are very common in people with AML. But if treated early, nearly all infections respond to appropriate treatment.

You may be advised to:

* take regular doses of antibiotics to prevent bacterial infections
* maintain good personal and dental hygiene
* avoid contact with anyone who's known to have an infection – even if it's a type of infection that you were previously immune to, such as chickenpox or measles
* check with your GP to make sure your vaccinations are up-to-date – you will not be able to have any vaccine that contains "live" viruses or bacteria, such as the shingles vaccine and MMR vaccine (against measles, mumps and rubella)

Report any possible symptoms of an infection to your treatment unit immediately as prompt treatment may be needed to prevent complications.

Symptoms of an infection can include:

* a sore throat
* a high temperature, and feeling hot or shivery (fever)
* flu-like symptoms, such as headaches, aching muscles and tiredness
* breathlessness or a cough
* pain when peeing

## **Bleeding**

If you have AML, you might bleed and bruise more easily because of the low levels of platelets (clot-forming cells) in your blood. Bleeding may also be excessive.

People with advanced AML are more vulnerable to excessive bleeding inside their body.

Serious bleeding can occur:

* inside the skull (intracranial haemorrhage) – causing symptoms such as a severe headache, stiff neck, vomiting and confusion
* inside the lungs (pulmonary haemorrhage) – causing symptoms such as coughing up blood, breathing difficulties and a bluish skin tone (cyanosis)
* inside the stomach (gastrointestinal haemorrhage) – causing symptoms such as vomiting blood and passing poos that are very dark or tar-like in colour

All these types of haemorrhage should be regarded as medical emergencies.

## **Infertility**

Most treatments used to treat AML can cause infertility. This is often temporary, but in some cases can be permanent.

People particularly at risk of permanent infertility are those who have received high doses of chemotherapy and radiotherapy in preparation for a bone marrow or stem cell transplant.

Your treatment team can talk to you about the risk of infertility in your specific circumstances and discuss any fertility options before you begin your treatment.

**EPIDEMIOLOGY**

Cancer Incidence Overview:

According to the World Health Organization, cancer claimed the lives of 41,000 Nigerians in 2018 out of

166,000 cases documented in the country. Nigeria was responsible for around 15.0% of Africa's estimated

681,000 new cancer cases in 2008. About 100,000 new cancer cases in Nigeria occur yearly

(Ferlay et al.,2010). The main reason for the significant increase in new cancer cases in Nigeria is; alcohol consumption,tobacco use, unhealthy diet, sedentary lifestyle, and polluted environments. Breast cancer, cervical cancer,prostate cancer,and blood cancer are Nigeria's standard and most prevalent cases

. Breast cancer is recognized as a significant cause of morbidity and mortality in Nigeria (Jedy-Agba et al., 2012).

Breast cancer remains the leading cause of death among African women(Tsoka-Gwegwenia et al., 2017).

A retrospective study conducted from January 2004 to December 2013 reported that 3,314 new cases of

Cancer was recorded in Lagos University Teaching Hospital (LUTH) during the study period. The mean age of cancer presentation is 48.52 ±16.44 years, and the male-to-female ratio was 1:3 (Sowunmi et al.,2018).Breast (38.1%), cervical (17.0%),and colorectal cancers (3.3%) are the most common ones recorded (Sowunmi et al., 2018). Another study found that 1436 (4.74%) cancer deaths out of 30287 deaths were recorded from death registers in the wards and mortuary over 14 years (2000–2013). The male-to-female

ratio was 1: 2.2. Overall, breast cancer was responsible for most deaths (Akinde et al., 2015).In other wealthy countries, the gender distribution is highly similar, but this ratio is exceptional (Wireduand Armah, 2006). Another 6-year (2014-2019) descriptive retrospective study conducted in the State tertiary health care center

in Delta State, Nigeria, reported that Cancer accounted for 668 (28.9%) of 2300 histologically diagnosed

cases, involving 461 females and 207 males with mean ages of 48.40 and 54.14 respectively. The combined sex mean age and age ranges were 50.17 and 1-98 years,respectively(Uchendu,2020).Themost

common cancers are breast (36.5%), colorectal (11.7%), prostate (8.1%), cervical (7.2%), soft tissue(6.0%), non-melanoma skin (5.2%), ovarian (4.0%),metastatic (4.0%), gastric (2.6%), thyroid (1.8%), and

salivary gland (1.4%) cancers (Uchendu, 2020).

A study from Ghana report Breast,cervical, hematolymphoid, cervical, prostate, liver, and colorectal malignancies as the most common type of

cancer (Wiredu & Armah, 2006).

Data from 2 population -based cancer registries(PBCRs )in Nigeria [Ibadan Population-Based Cancer Registry (IBCR) and the Abuja Population-Based Cancer Registry (ABCR)], covering two years 2009

–2010, a total of 3393 cancer cases were reported by the IBCR. Of these cases, 34.0% (1 155) were seen among males and 66% (2 238) in females. In Abuja, over the same period, 1128 invasive cancers

were reported. 33.6% (389) of these cases were males ,and 66.4%(768)infemales. The Mean age of diagnosis of all cancers in men for Ibadan and Abuja was 51.1 and 49.9 years, respectively. For women, the mean age of all cancers diagnosed in Ibadan and Abuja was 49.1 and 45.4, respectively (Jedy-Agba et al.,2012). Breast and cervical cancer were the most typical cancers among women, and prostate cancer was the most common among men (Jedy-Agba et al.,2012).Another study conducted between Nigeria and neighboring countries (Benin, Cameroun, Chad,Niger) found that the most common male cancer in Nigeria and border countries are Prostate cancer, seconded by Liver. In this study, also we found Breast cancer to be the most common in females, followed by

Cervical Cancer. Larynx and Kaposi sarcoma are the least common cancer for both males and females in the

population (Baba et al., 2018).A study reviewed clinical records of confirmed breast cancer patients between January 2011 and December 2015 at the Ekiti State University Teaching Hospital,Nigeria, found that eighty two breast cancer patients were seen. Their ages ranged from 26-95 years (mean48.9±14.9years,median 47.5 years).Eighty-one(98.8%) were females, and the majority (65.4%) were premenopausal (Olaogun et al., 2020). Between 2012 and 2014, the PBCRs reported

4,336 incident cancer cases, including 1,627(37.5%)malesand2,709(62.5%) females. Infections were linked to 1,030(23.8%) of these malignancies, while 951 (22.0%)were caused by infections. Cervical and liver cancers,

non-lymphoma,and Hodgkin's Were The Most Common Infection-related cancers HPV,EBV

November-December, 2022 hepatitis B and C, HIV, and HHV8 were the most common infectious agents linked to cancer in this population (Odutola et al.,2016).According to aten-year assessment of Port Harcourt cancer registry data,males accounted for 1,191 (44.4%) of the 2,682 malignancies recorded, while females accounted for 1,491 (55.6%). The average age of the participants was 51.9 years. Breast cancer (29.0%), prostate cancer(25.2%),cervix cancer (6.6%),colorectal cancer (5.4%), and leukemia (4.3%) were the five most prevalent cancer locations (Christopher et al. 2019).Patients of African ancestry have the poorest outcome

and the shortest survival rates from cancer globally. This could be attributed to many variables

,including racial, biological, socioeconomic,and socio-cultural factors, which may be responsible for this

significant health problem (Bahnassy et al., 2020).

MostCommon Cancer Type in Nigeria:

•Breast cancer

•Prostate cancer

•Cervix Uteri

•Colorectal cancer

•Non-Hodgkin lymphoma

•Liver cancer

•Leukemia

•Ovarian Cancer

**RECENT GUIDELINE FROM NCI**

Leukaemia leads to the overproduction of abnormal white blood cells. These abnormal cells usually can’t carry out the normal functions of white blood cells. They crowd the bone marrow and spill into the blood and may then spread into organs such as the lymph nodes, spleen, liver, the brain and spinal cord, lungs, kidneys and testicles, where they can keep other cells in the body from doing their jobs.

Symptoms of leukaemia are notoriously vague and non-specific. This is partly responsible for the late detection and high mortality in Nigeria. It is therefore important for everyone to be aware of these symptoms and to report promptly to the hospital for evaluation. In leukaemia symptoms are more commonly caused by lack of normal blood cells than by the presence of abnormal white cells. As the bone marrow becomes full of leukaemia cells, it is unable to produce the large numbers of normal blood cells, which the body needs.

This leads to: Anaemia – due to lack of red blood cells, causing paleness, weakness, shortness of breath and tiredness; Recurrent infections – due to lack of normal white blood cells; Bleeding and bruising – due to lack of platelets. Other symptoms include Fever, Malaise (feeling unwell) and excessive sweating. In children, there may be pain in bones or joints. There may also be swelling of the belly due to enlargement of the liver (hepatomegaly) or the spleen (an organ of the immune system found just under the ribs on the left hand side) (splenomegaly).

Leukaemia results from damage to the DNA. The cause of this damage is unknown in most cases of leukaemia. However, there are certain ‘risk factors’ which increase the chance of developing leukaemia. These include: Gender – leukaemias are generally more common in males; Genetics – there is a slightly higher chance of development of some forms of leukaemia in close relatives of patients. Smoking; Chemotherapy or other medicines that weaken the immune system; and Certain genetic disorders like Down’s syndrome could also predispose an individual to the disease. Intense exposure to radiation, including radiotherapy for another condition can also lead to leukaemia.

For instance, many of the survivors of the atomic bomb used in World War II developed leukaemia due to the fall-out of radiation. However, no leukaemia has been linked to radiation from x-rays and CT scans.

Another important risk factor for leukaemia is exposure to certain chemicals such as benzene. It is instructive to note that according to the report of the United Nations Environment Programme (UNEP) released in August 2011 on its Environmental Assessment of Ogoniland, drinking water in some areas is contaminated with benzene, at levels 900 times above the WHO guideline.

In addition, benzene was detected in air samples at higher levels than stipulated by WHO. So one could imagine the number of people in these communities who are dying silently from leukaemia and other cancers related to environmental pollution. Most of these cases are never diagnosed due to absence of basic infrastructure for cancer care.

The current statistics of five (5) Nigerians dying of leukaemia every day is thus probably an underestimation. Sadly, the effect of this pollution will out-last the present generation.

The recent move by the Government of Nigeria to fast track the recommendations of UNEP, which had been ignored for four years is commendable. However, government must sustain the political will to ensure that the recommendations are followed through and not abandoned half way. All the other stakeholders, including the oil companies and the members of the affected communities should also play their roles in ensuring a comprehensive and sustained clean-up of these areas whilst preventing future contaminations, in Ogoniland and other oil-producing areas.

The gold standard for the treatment of some forms of leukaemia is stem cell transplant. A stem cell transplant is a procedure that replaces unhealthy stem cells with healthy ones. Stem cell transplant offers a potential cure for blood cancers such as leukemia, lymphoma, and other life-threatening diseases including aplastic anaemia and sickle cell anaemia.

A shining example of how this procedure can give a new lease of life to leukaemia patients is the Nigerian-American Oluwaseun Adebiyi. Thirty- two year old Seun is a graduate of the Yale Law School, a former corporate attorney at Goldman Sachs, and a trained pilot. Seun survived leukaemia (diagnosed a week before his 26th birthday), because he had access to stem cell transplant at the Memorial Sloan-Kettering Cancer Centre, in Manhattan, USA. That experience transformed and redirected his life.

Today he is a Project Manager of the American Cancer Society as well as the Founder/CEO of the Bone Marrow Registry in Nigeria (“BMRN”), Enugu. The BMRN is a not-for-profit organization established in 2012 to connect stem cell donors with patients who need stem cell transplant. If Seun had been in Nigeria rather than in the USA, he would most likely not be with us today.

In 2011, the University of Benin Teaching Hospital (UBTH) successfully pioneered stem cell transplantation in Nigeria. Unfortunately, the UBTH facility has fallen to desuetude, mainly because at five million naira per patient the cost of the procedure is beyond the reach of most Nigerians. Since inception four (4) years ago, only three (3) cases of Sickle Cell Anaemia have benefited from this procedure that is now available locally. Meanwhile, Nigeria has one of the highest incidences of sickle cell anemia in the world! No case of leukaemia has been treated. What a waste of scarce resources! Nigeria should as a matter of urgency provide subsidy to bring this life-saving treatment within the reach of the common man.

The sad situation at UBTH also underscores the importance of focusing first and foremost on prevention which is cheaper and surer. Even if the best of treatment were available, it would be useless if the illness is not diagnosed. It is important to note that the results of a simple blood count could help to diagnose leukaemia; yet most Nigerians get picked up late, leading to the high mortality. An excellent starting point in the effort to ensure access to optimal, accessible and affordable preventive healthcare is through the use of the Mobile Cancer Centres (MCC), as being championed by Committee Encouraging Corporate Philanthropy (CECP-Nigeria) for the BIG War Against Cancer.

CECP’s operational partner for the BIG War Against Cancer is the National Cancer Prevention Programme (NCPP), a non-governmental initiative founded in 2007. Over 100,000 Nigerians have been directly screened and treated so far, and through the awareness created, the NCPP is helping to protect millions of Nigerians from cancer. This monumental effort has contributed immensely to the reduction of cervical cancer deaths in Nigeria from 26 daily in 2008 to 22 daily in 2012 (WHO data). The MCC will facilitate the process of scaling up this effort.

An MCC is much more than a Mobile Mammogram. Rather, it is a clinic on wheels, in which screening, follow-up and treatment (including surgeries), can take place. It includes facilities for mammography, sonology, colonoscopy, colposcopy and cryotherapy, as well as a surgical theatre. It is also equipped with facilities for screening against most common diseases, including the Ten Major Cancer-related killer diseases (Diabetes, Renal Disease, Obesity, Malaria, Schistosomiasis, Helicobacter pylori, Hepatitis, HIV/AIDS, Human Papillomavirus (HPV) and Hypertension). Thus the MCC would tackle the double burden of disease, i.e. Communicable & Non-Communicable.

The MCC is perhaps the single most important means of raising the life expectancy of Nigeria which is currently the 12th lowest globally. Cancer and these ten disease conditions are the main culprits responsible for this low life expectancy. A single MCC in a state of Nigeria could make a huge positive difference. That state would be divided into smaller units such that every community would be reached by the Mobile Cancer Centre at least once a year.

The cost of one MCC is $600,000 only (about N120, 000, 000 at the current exchange rate) and its operational cost for one year (including cost of personnel, supplies and maintenance), is $685,000.

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**ACUTE LYMPHOCYTIC LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Acute lymphocytic leukemia (ALL) is a type of cancer of the blood and bone marrow — the spongy tissue inside bones where blood cells are made.

The word "acute" in acute lymphocytic leukemia comes from the fact that the disease progresses rapidly and creates immature blood cells, rather than mature ones. The word "lymphocytic" in acute lymphocytic leukemia refers to the white blood cells called lymphocytes, which ALL affects. Acute lymphocytic leukemia is also known as acute lymphoblastic leukemia.

Acute lymphocytic leukemia is the most common type of cancer in children, and treatments result in a good chance for a cure. Acute lymphocytic leukemia can also occur in adults, though the chance of a cure is greatly reduced.

**Causes**

Acute lymphocytic leukemia occurs when a bone marrow cell develops changes (mutations) in its genetic material or DNA. A cell's DNA contains the instructions that tell a cell what to do. Normally, the DNA tells the cell to grow at a set rate and to die at a set time. In acute lymphocytic leukemia, the mutations tell the bone marrow cell to continue growing and dividing.

When this happens, blood cell production becomes out of control. The bone marrow produces immature cells that develop into leukaemia white blood cells called lymphoblasts. These abnormal cells are unable to function properly, and they can build up and crowd out healthy cells.

It's not clear what causes the DNA mutations that can lead to acute lymphocytic leukemia.

**Risk factors**

Factors that may increase the risk of acute lymphocytic leukemia include:

* **Previous cancer treatment.** Children and adults who've had certain types of chemotherapy and radiation therapy for other kinds of cancer may have an increased risk of developing acute lymphocytic leukemia.
* **Exposure to radiation.** People exposed to very high levels of radiation, such as survivors of a nuclear reactor accident, have an increased risk of developing acute lymphocytic leukemia.
* **Genetic disorders.** Certain genetic disorders, such as Down syndrome, are associated with an increased risk of acute lymphocytic leukemia.

**Symptoms**

Signs and symptoms of acute lymphocytic leukemia may include:

* Bleeding from the gums
* Bone pain
* Fever
* Frequent infections
* Frequent or severe nosebleeds
* Lumps caused by swollen lymph nodes in and around the neck, armpits, abdomen or groin
* Pale skin
* Shortness of breath
* Weakness, fatigue or a general decrease in energy

**DIAGNOSIS AND TEST**

Tests and procedures used to diagnose acute lymphocytic leukemia include:

* **Blood tests.** Blood tests may reveal too many or too few white blood cells, not enough red blood cells, and not enough platelets. A blood test may also show the presence of blast cells — immature cells normally found in the bone marrow.
* **Bone marrow test.** During bone marrow aspiration and biopsy, a needle is used to remove a sample of bone marrow from the hipbone or breastbone. The sample is sent to a lab for testing to look for leukemia cells.  
  Doctors in the lab will classify blood cells into specific types based on their size, shape, and other genetic or molecular features. They also look for certain changes in the cancer cells and determine whether the leukemia cells began from B lymphocytes or T lymphocytes. This information helps your doctor develop a treatment plan.
* **Imaging tests.** Imaging tests such as an X-ray, a computerized tomography (CT) scan or an ultrasound scan may help determine whether cancer has spread to the brain and spinal cord or other parts of the body.
* **Spinal fluid test.** A lumbar puncture test, also called a spinal tap, may be used to collect a sample of spinal fluid — the fluid that surrounds the brain and spinal cord. The sample is tested to see whether cancer cells have spread to the spinal fluid.

### **Determining your prognosis**

Your doctor uses information gathered from these tests and procedures to determine your prognosis and decide on your treatment options. Other types of cancer use numerical stages to indicate how far the cancer has spread, but there are no stages of acute lymphocytic leukemia.

Instead, the seriousness of your condition is determined by:

* The type of lymphocytes involved — B cells or T cells
* The specific genetic changes present in your leukemia cells
* Your age
* Results from lab tests, such as the number of white blood cells detected in a blood sample

**Treatment**

In general, treatment for acute lymphocytic leukemia falls into separate phases:

* **Induction therapy.** The purpose of the first phase of treatment is to kill most of the leukemia cells in the blood and bone marrow and to restore normal blood cell production.
* **Consolidation therapy.** Also called post-remission therapy, this phase of treatment is aimed at destroying any remaining leukemia in the body.
* **Maintenance therapy.** The third phase of treatment prevents leukemia cells from regrowing. The treatments used in this stage are usually given at much lower doses over a long period of time, often years.
* **Preventive treatment to the spinal cord.** During each phase of therapy, people with acute lymphocytic leukemia may receive additional treatment to kill leukemia cells located in the central nervous system. In this type of treatment, chemotherapy drugs are often injected directly into the fluid that covers the spinal cord.

Depending on your situation, the phases of treatment for acute lymphocytic leukemia can span two to three years.

Treatments may include:

* **Chemotherapy.** Chemotherapy, which uses drugs to kill cancer cells, is typically used as an induction therapy for children and adults with acute lymphocytic leukemia. Chemotherapy drugs can also be used in the consolidation and maintenance phases.
* **Targeted therapy.** Targeted drug treatments focus on specific abnormalities present within cancer cells. By blocking these abnormalities, targeted drug treatments can cause cancer cells to die. Your leukemia cells will be tested to see if targeted therapy may be helpful for you. Targeted therapy can be used alone or in combination with chemotherapy for induction therapy, consolidation therapy or maintenance therapy.
* **Radiation therapy.** Radiation therapy uses high-powered beams, such as X-rays or protons, to kill cancer cells. If the cancer cells have spread to the central nervous system, your doctor may recommend radiation therapy.
* **Bone marrow transplant.** A bone marrow transplant, also known as a stem cell transplant, may be used as consolidation therapy or for treating relapse if it occurs. This procedure allows someone with leukemia to reestablish healthy bone marrow by replacing leukemic bone marrow with leukemia-free marrow from a healthy person.  
  A bone marrow transplant begins with high doses of chemotherapy or radiation to destroy any leukemia-producing bone marrow. The marrow is then replaced by bone marrow from a compatible donor (allogeneic transplant).
* **Engineering immune cells to fight leukemia.** A specialized treatment called chimeric antigen receptor (CAR)-T cell therapy takes your body's germ-fighting T cells, engineers them to fight cancer and infuses them back into your body.  
  CAR-T cell therapy might be an option for children and young adults. It might be used for consolidation therapy or for treating relapse.
* **Clinical trials.** Clinical trials are experiments to test new cancer treatments and new ways of using existing treatments. While clinical trials give you or your child a chance to try the latest cancer treatment, the benefits and risks of the treatment may be uncertain. Discuss the benefits and risks of clinical trials with your doctor.

### **Treatment for older adults**

Older adults, such as those older than 65, tend to experience more complications from treatments. And older adults generally have a worse prognosis than children who are treated for acute lymphocytic leukemia.

Discuss your options with your doctor. Based on your overall health and your goals and preferences, you may decide to undergo treatment for your leukemia.

Some people may choose to forgo treatment for the cancer, instead focusing on treatments that improve their symptoms and help them make the most of the time they have remaining.

**Alternative medicine**

No alternative treatments have been proved to cure acute lymphocytic leukemia. But some alternative therapies may help ease the side effects of cancer treatment and make you or your child more comfortable. Discuss your options with your doctor, as some alternative treatments could interfere with cancer treatments, such as chemotherapy.

Alternative treatments that may ease symptoms include:

* Acupuncture
* Exercise
* Massage
* Meditation
* Relaxation activities, including yoga and tai chi

### **When to see a doctor**

Make an appointment with your doctor or your child's doctor if you notice any persistent signs and symptoms that concern you.

Many signs and symptoms of acute lymphocytic leukemia mimic those of the flu. However, flu signs and symptoms eventually improve. If signs and symptoms don't improve as expected, make an appointment with your doctor.

**DIFFERENTIAL DIAGNOSIS**

* B cell lymphoma
* Acute myeloid leukemia
* Non-Hodgkin lymphoma

**EPIDEMIOLOGY**

It is diagnosed in about 4000 people in the United States each year, with the majority being under the age of 18. It is the most common malignancy of childhood. The peak age of diagnosis is between two and ten years of age.

Acute Lymphocytic Leukemia is more common in children with Trisomy 21 (Down syndrome), neurofibromatosis type 1, Bloom syndrome, and ataxia telangiectasia. All are common in children between two and three years of age. Prognosis is diminished in children when diagnosed in infants less than one year of age and in adults. It is more favorable in children. The association of the MLL gene in children at the 11q23 chromosome is associated with poor prognosis. Acute lymphocytic leukemia is a disease with low incidence overall in population studies. The incidence of acute lymphocytic leukemia is about 3.3 cases per 100,000 children. Survival rates for ALL have improved dramatically since the 1980s, with a current five-year overall survival rate estimated at greater than 85 percent.

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**ACUTE MYELOGENOUS LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Acute myelogenous leukemia, also called AML, is a cancer of the blood and bone marrow. Bone marrow is the soft matter inside bones where blood cells are made.

The word "acute" in acute myelogenous leukemia means the disease tends to get worse quickly. It's called myelogenous (my-uh-LOHJ-uh-nus) leukemia because it affects cells called the myeloid cells. These typically develop into mature blood cells, including red blood cells, white blood cells and platelets.

AML is the most common type of acute leukemia in adults. The other type is acute lymphoblastic leukemia, also called ALL. Although AML can be diagnosed at any age, it is less common before age 45. AML also is called acute myeloid leukemia, acute myeloblastic leukemia, acute granulocytic leukemia and acute nonlymphocytic leukemia.

Unlike other cancers, there are no numbered stages of acute myelogenous leukemia.

**Causes**

It's often not clear what causes acute myelogenous leukemia.

Healthcare professionals know that it starts when something causes changes to the DNA inside cells in the bone marrow. The bone marrow is the spongy material inside bones. It's where blood cells are made.

The changes that lead to acute myelogenous leukemia are thought to happen in cells called myeloid cells. Myeloid cells are bone marrow cells that can turn into the blood cells that circulate through the body. Healthy myeloid cells can become:

* Red blood cells, which carry oxygen to the body.
* Platelets, which help stop bleeding.
* White blood cells, which help fight infections.

Every cell in the body contains DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time. But when the DNA changes happen in the myeloid cells, the changes give different instructions. The myeloid cells start to make a lot of extra cells, and they don't stop.

The DNA changes cause the myeloid cells to make a lot of immature white blood cells, called myeloblasts. The myeloblasts don't work right. They can build up in the bone marrow. They can crowd out healthy blood cells. Without enough healthy blood cells, there might be low oxygen levels in the blood, easy bruising and bleeding, and frequent infections.

**Risk factors**

Factors that may increase the risk of acute myelogenous leukemia, also called AML, include:

* **Older age.** Acute myelogenous leukemia is most common in adults age 65 and older.
* **Prior cancer treatment.** People who've had certain types of chemotherapy and radiation therapy may have a greater risk of AML.
* **Radiation exposure.** People exposed to very high levels of radiation, such as a nuclear reactor accident, have an increased risk of developing AML.
* **Dangerous chemical exposure.** Certain chemicals, such as benzene, are linked to a greater risk of AML.
* **Smoking cigarettes.** AML is linked to cigarette smoke, which contains benzene and other known cancer-causing chemicals.
* **Other blood disorders.** People who've had another blood disorder, such as myelodysplasia, myelofibrosis, polycythemia vera or thrombocythemia, are at greater risk of AML.
* **Genetic disorders.** Certain genetic disorders, such as Down syndrome, are associated with an increased risk of AML.
* **Family history.** People with a close blood relative, such as a sibling, parent or grandparent with a blood or bone marrow disorder are at higher risk for AML.

Many people with AML have no known risk factors, and many people who have risk factors never develop cancer.

**Symptoms**

Symptoms of acute myelogenous leukemia may include:

* Fever.
* Pain. Common places for pain include the bones, back and stomach.
* Feeling very tired.
* Paleness or change in skin color.
* Frequent infections.
* Easy bruising.
* Bleeding with no clear cause, such as in the nose or gums.
* Shortness of breath.

**DIAGNOSIS AND TEST**

Acute myeloid leukemia diagnosis often begins with an exam that checks for bruising, bleeding in the mouth or gums, infection, and swollen lymph nodes. Other tests include blood and lab tests, bone marrow biopsy, lumbar puncture, and imaging.

Tests and exams to diagnose acute myelogenous leukemia, also called AML, include:

### **Blood tests**

Blood tests for acute myelogenous leukemia might include a test to count the number of blood cells in a sample of blood. This test is called a complete blood count. The results may show too many or too few white blood cells. Often the test finds that there are not enough red blood cells and not enough platelets. Another blood test looks for immature white blood cells called myeloblasts in the blood. These cells typically aren't found in the blood. But they can occur in the blood of people with AML.

### **Bone marrow aspiration and biopsy**

Bone marrow aspiration and biopsy are procedures that involve collecting cells from the bone marrow. In bone marrow aspiration, a needle is used to draw a sample of the bone marrow fluid. In a bone marrow biopsy, a needle is used to collect a small amount of solid tissue. The samples are typically taken from the hip bone. The samples go to a lab for testing.

In the lab, tests can look for DNA changes in the bone marrow cells. Which DNA changes are present in your bone marrow cells are an important part of diagnosing AML. The results can help your healthcare team create a treatment plan.

### **Lumbar puncture**

Sometimes, a lumbar puncture may be needed if there's concern that the leukemia has spread to the brain and spinal cord. A lumbar puncture also is called a spinal tap. It removes a sample of the fluid that surrounds the brain and spinal cord. A small needle is inserted into the lower back to remove a fluid sample. The sample is sent to a lab.

### **Imaging tests**

Imaging tests make pictures of the body. For AML, imaging tests might make pictures of the brain, if there's concern that the leukemia cells have spread there. Imaging might include CT or MRI. If there's concern that the leukemia might have spread to another part of the body, imaging might be done with a positron emission tomography scan, also called a PET scan.

### **Your AML subtype**

If you're diagnosed with AML, you may need further lab tests to determine your AML subtype. These tests include examining your blood and bone marrow for genetic changes and other signs that indicate specific AML subtypes. Currently, there are 15 different subtypes. Your AML subtype helps your healthcare professional determine the best treatment for you.

**Treatment**

Many types of treatment exist for acute myelogenous leukemia, also called AML. Treatment depends on several factors, including the subtype of the disease, your age, your overall health, your prognosis and your preferences.

Treatment usually has two phases:

* **Remission induction therapy.** This first phase aims to kill the leukemia cells in your blood and bone marrow. But it doesn't usually destroy all the leukemia cells. You will need further treatment to keep the disease from coming back.
* **Consolidation therapy.** This phase also is called post-remission therapy or maintenance therapy. It aims to kill the remaining leukemia cells. Consolidation therapy is crucial to helping lower the risk of relapse.

Treatments include:

**Chemotherapy.** Chemotherapy treats cancer with strong medicines. Most chemotherapy medicines are given through a vein. Some come in pill form. Chemotherapy is the main type of remission induction therapy. It also may be used for consolidation therapy.

People with AML usually stay in the hospital during chemotherapy treatments because the medicines kill many healthy blood cells while destroying leukemia cells. If the first chemotherapy cycle doesn't cause remission, it can be repeated.

Side effects of chemotherapy depend on the medicines you're given. Common side effects are nausea and hair loss. Serious, long-term complications may include heart disease, lung damage, fertility problems and other cancers.

**Targeted therapy.** Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Your leukemia cells will be tested to see if targeted therapy may be helpful for you. Targeted therapy may be used alone or in combination with chemotherapy during induction therapy.

**Bone marrow transplant.** A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments. A bone marrow stem cell transplant may be used for both remission induction and consolidation therapy.

Before a bone marrow transplant, you receive very high doses of chemotherapy or radiation therapy to destroy your leukemia-producing bone marrow. Then you receive infusions of stem cells from a compatible donor. This is called an allogeneic transplant.

There is an increased risk of infection after a transplant.

**Alternative medicine**

No alternative treatments have been found to treat acute myelogenous leukemia. But integrative medicine may help you cope with the stress of a cancer diagnosis and side effects of your treatment.

Alternative treatments that may help relieve symptoms include:

* Acupuncture.
* Exercise.
* Massage.
* Meditation.
* Relaxation activities, such as yoga.
* Art and music therapy.

### **When to see a doctor**

Make an appointment with your healthcare professional if you have ongoing symptoms that worry you. Acute myelogenous leukemia symptoms are like those of many more-common conditions, such as infections. The healthcare professional may check for those causes first.

## **Outlook / Prognosis**

Currently, allogeneic stem cell transplantation is the only way to cure acute myeloid leukemia. Depending on your situation, your provider may recommend stem cell transplantation as your first AML treatment or if you have AML that comes back within 12 months. Unfortunately, not everyone may be a candidate for stem cell transplantation.

#### **What is the prognosis for AML?**

There are two sides of the coin in acute myeloid leukemia prognosis. One side is complete remission. The other is recurrence, when AML comes back:

* Overall, an estimated 50% to 80% of people with acute myeloid leukemia achieve complete remission after treatment. Complete remission happens more often in children and people under age 60. Remission may last for months or years.
* About 50% of people who achieve complete remission develop recurrent AML. When that happens, providers may recommend additional chemotherapy or stem cell transplantation. They may suggest participation in a clinical trial.

If you or your child has AML, ask your provider to explain what you can expect.

#### **What is the survival rate of acute myeloid leukemia?**

Acute myeloid leukemia is a complicated illness. There are several AML subtypes, which makes it difficult to be specific about survival rates.

For example, the five-year survival rate for children under age 15 is 67%. But some research suggests that the five-year survival rate increases to more than 80% in children who have the APL subtype. And age makes a difference. In general, 30% of adults with acute myeloid leukemia are alive five years after diagnosis. Remember, AML typically affects people age 60 and older who may have other health issues.

It’s important to remember that survival rates reflect the experiences of large groups of people with AML. In this case, survival rate data includes survival rates from 2012 to 2018, and there are some new and more effective treatments for AML.

Many things affect how long you’ll live with acute myeloid leukemia. That means your healthcare providers, the people who know your medical history and your overall health, are your best resources for information.

## **Prevention**

No, you can’t prevent acute myeloid leukemia. Experts know that genetic mutations cause acute myeloid leukemia but they don’t know what triggers them. They do know about risk factors that may cause AML. Risk factors you can modify include:

* Smoking, including exposure to second-hand smoke. If you smoke, try to quit. If you live or work around someone who smokes, try to limit how much time you spend with them when they’re smoking.
* Long-term exposure to certain carcinogenic chemicals, particularly benzene and formaldehyde. If you work around these carcinogens, be sure you follow all safety precautions, such as wearing protective clothing.

## **Living With**

It’s not easy to live with cancer that may come back. Getting involved with cancer survivorship programs is one way to take care of yourself. You may not be able to keep acute myeloid leukemia from coming back. But you can take steps to be as healthy as possible, no matter what. Here are some suggestions:

* Treatments for acute myeloid leukemia may affect your diet. You need to eat well to stay strong. If you’re having trouble eating, ask to speak to a nutritionist.
* AML treatment side effects can be hard to manage. If you need to, talk to your provider about palliative care.
* Cancer is stressful. You may be able to manage stress with exercise. But check with your provider before starting a new or aggressive exercise program.
* Cancer can be lonely. AML is a rare disease. You may feel anxious about discussing your situation. In that case, consider joining a support group.
* Acute myeloid leukemia can be exhausting. Treatment may sap your energy. Try to remember to get as much sleep as you need.

**DIFFERENTIAL DIAGNOSIS**

Other diseases with presentations similar to AML include Acute lymphoblastic leukemia, anemia, aplastic anemia, B-cell lymphoma, bone marrow failure, chronic myelogenous leukemia, lymphoblastic lymphoma, MDS, myelophthisic anemia, and primary myelofibrosis.

**EPIDEMIOLOGY**

The annual incidence of new cases in both men and women is approximately 4.3 per 100,000 population, totaling over 20,000 cases per year in the United States alone. The median age at the time of diagnosis is about 68, with a higher prevalence observed among non-Hispanic Whites. Furthermore, males exhibit a higher incidence compared to females, with a ratio of 5:3.

## 

## **Updates on Treatments in Newly Diagnosed AML**

## The classical paradigm to achieve cure in AML is first to induce CR thereby reducing the leukemia burden by several orders of magnitude, followed by post‐remission therapy in the form of chemotherapy and/or alloSCT. The choice of the most appropriate induction and post‐remission therapy is based on multiple parameters, including patient comorbidities, past medical history including prior myeloid disease and/or cytotoxic chemotherapy exposure, AML cytogenetic and molecular risk profile, possibly post‐therapy MRD status, as well as donor availability and patient goals of care. Historically, the first step for deciding on initial treatment is based on patients 'fitness for intensive therapy, with intensive chemotherapy induction being the default for those who are being deemed fit for a highly myelosuppressive/gut‐toxic approach. It is perhaps easier to delineate who should not receive intensive chemotherapy than who should definitely be subject to a long hospitalization with a significant risk of treatment‐related mortality. At this time, age over 75 is thought to be a relative contraindication to intensive chemotherapy, especially based on the known availability of effective less intensive chemotherapy. Other than age, the FDA has adopted a set of stringent criteria (poor hepatic, renal, cardiac, and pulmonary function) to definitively consider a patient unfit for intensive chemotherapy. The criteria are commonly incorporated into eligibility criteria and were validated in a large cohort of patients for predicting shorter‐term mortality after intensive chemotherapy treatment in AML. However, with multiple therapeutics emerging in recent years, the paradigm has shifted toward “who would benefit from intensive chemotherapy” rather than who is deemed fit. For instance, even a ‘fit’ patient (of any age) with adverse risk biology might not be “appropriate” for intensive chemotherapy due the likelihood of poor outcomes. The dilemma is most prominent in patients aged 60–75 years, which represents the largest age group in AML, many of whom can potentially be treated with either intensive or less‐intensive therapies in the upfront setting. We will elaborate on the various therapeutic possibilities and present our approach, including an updated suggested therapeutic algorithm for patients in this age group.

### 6.2. Updates on Intensive Therapy for Newly Diagnosed Patients

### The backbone of intensive chemotherapy remains an anthracycline‐ and cytarabine‐based approach, most commonly as the “7 + 3” regimen using daunorubicin at a dose of 60–90 mg/m2 for 3 days and cytarabine at a dose of 100–200 mg/m2 for 7 days. However, other induction regimens in use include CLAG‐M, G‐CLAM, IA, FLAG‐IDA, and lomustine‐IA. Whether any of these are ‘better’ than 3 + 7 alone is unclear, though the addition of either lomustine, a nucleoside analog, or treatment with FLAG‐IDA have each been suggested to be superior to 3 + 7 in prospective randomized trials; however, the latter was deemed too toxic for general use. Moreover, several drugs were recently approved (in combination with chemotherapy) for patients with newly diagnosed (ND) AML who are fit for intensive chemotherapy. Regarding the dose of daunorubicin, in two large‐randomized trials, 90 versus 45 mg/m2 improved survival among younger and older patients, as well as in patients with specific mutations (*NPM1*, *FLT3*, and *DNMT3A*). However, there was no benefit in term of survival among 1206 patients with AML when 90 mg/m2 was compared to 60 mg/m2 (although all patients received a second course of daunorubicin 50 mg/m2, which could potentially reduce the beneficial effects of 90 vs. 60 mg/m2). The two‐step randomized DAUNODOUBLE trial evaluated daunorubicin intensity and the additive value of second induction in 864 patients aged 18–65 years with ND AML treated with intensive chemotherapy. In the first randomization, there was no difference in response or survival in patients treated with 60 mg/m2 compared with 90 mg/m2 (composite CR rates: 90% vs. 89%, *p* = 0.691; 3‐year OS 65% vs. 58%, *p* = 0.242, respectively). In subgroup analyses, comparable outcomes were seen across patients with *NPM1*, *FLT3‐*ITD, and all ELN 2017 risk groups. In the second randomization, there was no benefit of a second induction among the 389 who achieved a good early response (defined as < 5% blasts in the day‐14 bone marrow evaluation): composite CR rates 87% versus 85%; 3‐year OS 76% versus 75% with one vs. two inductions, respectively.

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### **Acute promyelocytic leukemia (APL)**

**DEFINITION AND DESCRIPTION**

Acute promyelocytic leukemia (APL) is a rare blood cancer. It’s a form of acute myeloid leukemia that happens when a genetic mutation (change) creates abnormal white blood cells that multiply uncontrollably in your bone marrow. Healthcare providers may call this condition APL leukemia or M3-leukemia.

APL is a serious condition with life-threatening symptoms, including excessive bleeding, which come on suddenly and quickly get worse. Thanks to treatment that’s an innovative combination of chemotherapy and non-chemotherapy drugs, healthcare providers can treat and often cure acute promyelocytic leukemia.

## **Symptoms and Causes**

Acute promyelocytic leukemia (APL) symptoms develop when your bone marrow can’t make normal numbers of red blood cells, white blood cells and platelets. If you have low blood cell levels (pancytopenia), you may develop serious symptoms, including anemia, bleeding issues (hemorrhage) and infections.

Other APL symptoms are:

* Fatigue from anemia, or low red blood cells.
* Frequent infections because you have low levels of infection-fighting white blood cells.
* Unintentional weight loss because your metabolism speeds up and you burn energy from food.

#### **Bleeding symptoms**

In acute promyelocytic leukemia, you don’t have enough platelets or blood clotting factors. Platelets slow or stop bleeding. Blood clotting factors help make clots in your blood. APL bleeding symptoms include:

* Bleeding from any site, including bleeding gums, nosebleeds or heavy menstrual bleeding.
* Bruising from blood pooling under your skin.
* Difficulty moving your arms and legs, headaches or vision issues from bleeding into your brain (intracranial hemorrhage).
* Poop that looks black or has red streaks of blood. This happens if you have bleeding in your gut (gastrointestinal bleeding).

### **Causes of acute promyelocytic leukemia**

This condition happens when two genes that drive blood cell development fuse to create the abnormal gene *PML-RARa*. You don’t inherit this genetic mutation (change). It happens randomly during your lifetime. Experts don’t know what triggers the change.

The mutation keeps white blood cells from developing as they should. The immature white blood cells (promyelocytes) multiply uncontrollably, crowding out healthy blood cells and platelets.

### **complications of APL**

APL can be life-threatening, causing severe bleeding that quickly gets worse. Contact a healthcare provider or go to the emergency department if you have bleeding that you can’t control, like bleeding from a cut or injury or there’s lots of blood in the toilet after you poop or pee or bleeding gums.

## **Diagnosis and Tests**

Healthcare providers typically order the following tests to diagnose this condition:

* Complete blood count (CBC): APL creates abnormal white blood cells. CBC tests show the number of blood cells and platelets in a blood sample.
* Peripheral blood smear: Providers may see high levels of granules or Auer rods inside promyelocytes, a specific type of white blood cell.
* Bone marrow biopsy: Providers order these to get samples of your bone marrow cells for analysis.
* Flow cytometry: In this test, pathologists examine the surface of abnormal cells, checking for specific protein patterns that confirm APL.
* Polymerase chain reaction (PCR) test: This test checks for the abnormal gene that causes APL.
* Cytogenetics: Pathologists will examine abnormal cells for specific changes in chromosomes. Finding those changes is how providers confirm an APL diagnosis.

Healthcare providers use white blood cell counts to classify cases as being low- or high-risk APL. People with high-risk acute promyelocytic leukemia are more likely to experience relapse (recurrent cancer).

## **Management and Treatment**

APL treatment is a combination of differentiation agents, chemotherapy and targeted therapy. This treatment combination, developed in the 1980s, transformed the condition from a fatal illness to a curable one.

Differentiation agents are non-chemotherapy treatments that help abnormal white blood cells mature (differentiate) into normal white blood cells. The non-chemotherapy treatment described below has increased the remission and cure rate to more than 95%.

Differentiation agents for APL are:

* All-trans-retinoic acid (ATRA), or tretinoin (Vesanoid®) — a form of vitamin A.
* Arsenic trioxide (ATO), a form of arsenic.

If your healthcare provider suspects you have APL, they’ll likely prescribe ATRA right away, even before tests confirm you have APL. Prompt treatment reduces the risk of life-threatening bleeding.

#### **APL treatment phases**

Treatment includes three phases: induction, consolidation and maintenance. Treatments vary, depending on risk:

* Induction: This phase focuses on eliminating enough leukemia cells to put APL into remission. Remission means you don’t have symptoms and tests don’t find signs of leukemia. Induction treatment uses a combination of a non-chemotherapy drug, chemotherapy and targeted therapy. You’ll need to stay in the hospital during induction, which usually lasts four to six weeks.
* Consolidation: Your oncologist may call this post-remission therapy. Consolidation treatment works to keep acute promyelocytic leukemia in remission and eliminate any remaining leukemia cells. This treatment uses the same drugs as induction treatment. You may receive treatment for eight months, with treatment sessions every two months. You may have treatment for four weeks and then a four-week treatment break. Treatment may be taking pills or receiving medication through an intravenous (IV) line.
* Maintenance: This is ongoing treatment in lower doses than induction and consolidation. Typically, people receive maintenance therapy for a year.

Your oncologist may combine treatment with supportive therapy like blood transfusions.

#### **Treatment complications**

The most common and serious complication is differentiation syndrome. This is a group of severe reactions to APL drugs. The reactions typically develop during the first three weeks of induction or initial treatment. Symptoms may be mild or severe and include:

* Cough.
* Excess fluid buildup around your heart and lungs (pleural effusion).
* Kidney failure (renal failure).
* Low blood pressure (hypotension).
* Low level of oxygen in your blood (hypoxemia).
* Shortness of breath (dyspnea).
* Swelling (inflammation) of your arms, legs and neck.
* Unexplained fever.
* Unexplained weight gain.

If you experience differentiation syndrome, your provider might stop treatment. They may use other drugs like hydroxyurea to bring down your white blood cell levels.

## **Outlook / Prognosis**

In general, the prognosis is good. While everyone’s situation is different, studies show between 90% and 95% of APL cases go into remission. APL can come back (recur) after treatment. Between 5% to 10% of people experience relapse, usually within the first three years after treatment, and need more or different treatment.

#### **Survival rates**

Acute promyelocytic leukemia is a rare disease, so what we know about survival rates comes from clinical trials involving people with low-risk and high-risk APL.

One analysis of clinical trials involving low-risk APL cases found that 99% of people were alive four years after treatment. Another analysis of research involving high-risk APL cases shows that 86% of people were alive after five years.

## **Living With**

Acute promyelocytic leukemia (APL) can come back (recur), so it’s important that you make it to your follow-up appointments.

You’ll probably have a check-up every month to two months for the first year after your treatment. After the first year, you’ll probably see your provider every three to four months for the next two years. Follow-up appointments may include tests like CBCs, PCRs and bone marrow biopsy.

#### **When should I go to the emergency room?**

APL can come back after treatment, causing symptoms that can get worse very quickly. If you’re in remission from acute promyelocytic leukemia, go to the emergency room right away if you have:

* Bleeding that you can’t control.
* Sudden pain and swelling in your legs or lower belly.

**DIFFERENTIAL DIAGNOSIS**

* Acute lymphoblastic leukemia (ALL)
* Acute myeloid leukemia (AML)
* Aplastic anemia
* Folic acid deficiency
* Myelodysplastic syndrome

**EPIDEMIOLOGY**

Acute promyelocytic leukemia is relatively rare and comprises about 7% to 8% of adult AML cases. Acute promyelocytic leukemia is usually seen in middle-aged people with a median age of 47 years. Acute promyelocytic leukemia occurs very rarely before the age of 20. The incidence is slightly higher in males than in females.

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**ACUTE ERYTHROID LEUKEMIA**

**DEFINITION AND DESCRIPTION**

A rare and aggressive variety of acute leukemia known as acute erythroid leukemia (AEL) primarily affects the creation of red blood cells. The rapid proliferation of abnormal and immature erythroid precursors in the bone marrow characterizes this subtype of acute myeloid leukemia (AML), which causes impaired blood cell production and various serious symptoms. The main features of acute erythroid leukemia, including its clinical characteristics, diagnosis, treatment options, and prognosis, will be covered in this article.

## **What Are the Clinical Features of Acute Erythroid Leukemia?**

Individuals can differ in their clinical characteristics of acute erythroid leukemia (AEL), a rare and aggressive subtype of acute myeloid leukemia (AML).

Nevertheless, some typical AEL clinical signs and symptoms include:

* Anemia: AEL frequently results in severe anemia, characterized by weakness, exhaustion, and pallor. This happens because the production of healthy red blood cells is hampered by the proliferation of abnormal erythroid precursors in the bone marrow.
* Thrombocytopenia: AEL can lower platelet counts, increasing the risk of bleeding and making bruising more likely.
* Neutropenia: This condition, characterized by a drop in healthy white blood cells, can increase a person's susceptibility to infections.
* Fever: Some AEL patients may experience a fever, which an infection or the disease itself may bring on.
* Bone Pain: The expansion of abnormal cells in the bone marrow can cause bone pain or discomfort in places like the sternum (breastbone) and long bones.
* Chronic Fatigue: Chronic fatigue is a common sign of AEL and is frequently brought on by anemia and the overall effects of leukemia on the body.
* Spleen Enlargement (Splenomegaly): AEL can result in spleen enlargement, which can cause abdominal pain or fullness.
* Weight Loss: Unpredictable weight loss is a sign of AEL that can occasionally be observed.
* Skin Pallor: Low platelet counts and anemia can both cause the skin to appear paler.
* Infections: Neutropenia (low white blood cell count), which increases the risk of infections, increases the possibility of recurrent or severe infections in people with AEL.
* Easy Bruising and Bleeding: Thrombocytopenia (low platelet count) can cause nosebleeds, easy bleeding after minor injuries, or prolonged bleeding.
* Headaches: Some people may experience headaches, which the illness or its side effects may bring on.

## **What Is the Classification of Acute Erythroid Leukemia?**

Based on the classification of the World Health Organization (WHO), AEL is divided into two major subtypes:

* Erythroleukemia (EL): Erythroid precursors and myeloblasts, or immature white blood cells, are found in the bone marrow in erythroleukemia (EL).
* Pure Erythroid Leukemia (PEL): In PEL, erythroid precursors make up more than 80 percent of the bone marrow cells, even though myeloblasts only account for about 20 percent of all cells.

## **Diagnosis of Acute Erythroid Leukemia**

To diagnose acute erythroid leukemia (AEL), a combination of clinical assessment, lab tests, and bone marrow examination is required. The main steps in the diagnostic procedure are as follows:

* Clinical Evaluation: A detailed physical examination and medical history are frequently the first steps in the diagnostic process. Healthcare professionals will ask about symptoms, previous illnesses, and any family members with blood disorders.
* Complete Blood Count (CBC): A CBC is a blood test that tells how many different blood cell types are in the bloodstream and their total number. Anemia (low red blood cell count), thrombocytopenia (low platelet count), and abnormal white blood cell counts are the most common abnormal blood cell counts associated with AEL. An examination of a blood sample under the microscope is called a peripheral blood smear. It enables the visual evaluation of blood cell characteristics and appearance.
* Peripheral Blood Smear: The peripheral blood of people with AEL may contain abnormal white blood cells and immature erythroid precursors (erythroblasts).
* Aspiration of Bone Marrow: A slender needle takes an aspirate, or liquid sample, from the bone marrow. It is determined how many erythroid precursors and myeloblasts are present in this sample by microscopically examining it.
* Bone Marrow Biopsy: Bone and bone marrow tissue are removed in small pieces during a bone marrow biopsy using a larger needle. Additionally, a microscopic examination of this tissue sample can reveal additional details about the degree of involvement and the presence of genetic abnormalities.
* Cytogenetic and Molecular Testing: Bone marrow samples can be used for genetic analysis to help pinpoint the precise genetic anomalies connected to AEL. AEL in children, for instance, is characterized by the t(1 22) translocation linked to the RBM15-MKL1 fusion gene. Additionally, molecular profiling can reveal details about genetic mutations that could influence treatment choices.
* Flow Cytometry: Flow cytometry is a laboratory method that can be used to recognize particular cell surface markers on leukemic cells. It helps to define the subtype and type of leukemia.

## **Treatment Options for Acute Erythroid Leukemia**

Acute erythroid leukemia (AEL) treatment options typically involve aggressive methods to induce remission and treat the illness' symptoms:

* Chemotherapy: The mainstay of AEL treatment consists of intensive chemotherapy regimens, frequently including cytarabine and anthracycline-based medications. Chemotherapy works by removing leukemic cells from the bone marrow to induce remission.
* Stem Cell Transplantation: Allogeneic stem cell transplantation may be considered for eligible patients, especially those with high-risk characteristics or those who achieve remission but are at a high risk of relapse. The possibility of long-term disease management is provided by stem cell transplantation.
* Supportive Care: AEL treatment is incomplete without supportive care techniques like blood transfusions to treat anemia and thrombocytopenia and control infections.
* Targeted Therapies: Emerging targeted and molecularly-guided therapies might be investigated based on genetic mutations and markers unique to each case, opening up potential paths for more individualized treatment plans.

## **Prognosis of Acute Erythroid Leukemia**

Age, general health, and the particular subtype of AEL all affect the prognosis for the disease. AEL typically has a worse prognosis than other AML subtypes. Poorer outcomes are more common in elderly patients and those with high-risk cytogenetic abnormalities. The likelihood of relapse is high, and survival in the long term is challenging, even though treatment strategies aim to achieve remission.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Acute Erythroid Leukemia (AEL) involves distinguishing it from several hematologic and non-hematologic conditions with overlapping clinical and morphologic features. Based on current WHO classification and expert sources, here are the key differential diagnoses and considerations:

Myelodysplastic Syndrome (MDS) with Erythroid Hyperplasia

* Cases with >50% erythroid precursors but <20% myeloblasts in non-erythroid cells are classified as MDS rather than AEL.
* Prominent dysplasia in multiple lineages supports MDS diagnosis.
* MDS with excess blasts may mimic erythroleukemia but generally has a lower blast count.

## Acute Myeloid Leukemia (AML) with Myelodysplasia-Related Changes

* If >50% of myeloid or megakaryocytic lineages show dysplasia, and blasts exceed 20% of non-erythroid cells, diagnosis favors AML with myelodysplasia-related changes rather than pure erythroid leukemia.
* Cytogenetic abnormalities typical of MDS are often present.

## Pure Erythroid Leukemia (PEL)

* A subtype of AEL where the erythroid lineage predominates exclusively (>80-90%) without significant myeloblast component.
* Needs to be distinguished from reactive erythroid hyperplasia and megaloblastic anemia.

## Megaloblastic Anemia

* Can mimic AEL morphologically due to erythroid hyperplasia and dysplasia.
* Distinguished by clinical context (nutritional deficiencies), vitamin B12/folate levels, and absence of clonal proliferation.

## Other Acute Leukemias

* Acute lymphoblastic leukemia (ALL) and other AML subtypes may have overlapping features but differ in immunophenotyping and lineage markers.

## Reactive Erythroid Hyperplasia

* Non-neoplastic increase in erythroid precursors due to anemia or marrow stress.
* Diagnosis of exclusion after ruling out clonal disorders.

## Acute Megakaryocytic Leukemia

* May resemble AEL morphologically but differs by expression of megakaryocytic markers (CD41, CD61).

## Other Poorly Differentiated Malignancies

* Small blue round cell tumors or carcinomas can rarely mimic marrow infiltration; immunophenotyping helps exclude these.

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**ACUTE MEGAKARYOBLASTIC LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Acute megakaryoblastic leukemia (AMKL) is a form of acute myeloid leukemia (AML) that occurs predominantly in childhood and particularly in children with Down syndrome (DS-AMKL). Nonspecific symptoms may be irritability, weakness, and dizziness while specific symptoms include pallor, fever, mucocutaneous bleeding, hepatosplenomegaly, neurological manifestations and rarely lymphadenopathy. Acute panmyelosis with myelofibrosis may also be associated with AMKL. In contrast to DS-AMKL (around 80 % survival), non-DS-AMKL is an AML subgroup associated with poor prognosis.

**Other Names for this Condition**

* Acute Megakaryocytic Leukemia
* AMKL (Acute Megakaryoblastic Leukemia)
* Myeloid Leukemia with Megakaryoblastic Maturation

## 

## **Symptoms of Megakaryocytic Leukemia**

Megakaryocytic Leukemia typically presents with symptoms related to abnormal blood cell production. Patients may experience a variety of general signs such as fatigue, easy bruising, and frequent infections. Other common symptoms include enlarged lymph nodes, unexplained weight loss, and bone pain. It is important to consult a healthcare provider for proper diagnosis and treatment if you experience these symptoms.

* Easy bruising
* Fatigue
* Frequent infections
* Bleeding gums
* Nosebleeds
* Petechiae (small red or purple spots on the skin)

## **Causes of Megakaryocytic Leukemia**

Megakaryocytic leukemia, also known as acute megakaryoblastic leukemia, is a rare type of leukemia that affects the blood and bone marrow. The main causes of this condition are related to genetic mutations that disrupt the normal development of blood cells, particularly megakaryocytes. These mutations can lead to uncontrolled growth and accumulation of abnormal megakaryocytic cells in the bone marrow, impairing the production of healthy blood cells.

Additionally, certain environmental factors and exposures may also play a role in the development of megakaryocytic leukemia. Early detection and prompt treatment are essential for managing this condition effectively.

* Genetic mutations
* Exposure to certain chemicals
* Radiation exposure
* Previous chemotherapy treatment
* Inherited genetic syndromes
* Viral infections

**Types of Megakaryocytic Leukemia**

Megakaryocytic Leukemia can manifest in different forms, each with its distinct characteristics. These forms may vary in terms of symptoms, prognosis, and treatment options. Understanding the types of Megakaryocytic Leukemia is crucial for proper diagnosis and management.

* **Acute Megakaryocytic Leukemia (AMKL)**: AMKL is a rare subtype of acute myeloid leukemia characterized by the excessive production of abnormal megakaryocytes in the bone marrow.
* **Chronic Megakaryocytic Leukemia**: Chronic Megakaryocytic Leukemia is a rare form of chronic myeloproliferative neoplasm where abnormal megakaryocytes accumulate in the bone marrow, leading to an overproduction of platelets.
* **Juvenile Myelomonocytic Leukemia (JMML)**: JMML is a childhood leukemia characterized by the proliferation of abnormal megakaryocytes and monocytes in the bone marrow, leading to increased production of white blood cells.
* **Myelofibrosis with Myeloid Metaplasia**: Myelofibrosis is a type of chronic leukemia where there is progressive scarring of the bone marrow leading to the overproduction of abnormal megakaryocytes and other blood cells.
* **Essential Thrombocythemia**: Essential Thrombocythemia is a chronic myeloproliferative neoplasm characterized by the overproduction of platelets by abnormal megakaryocytes, leading to an increased risk of blood clots and bleeding.

## **Risk Factors**

Megakaryocytic Leukemia, a rare type of blood cancer, has certain factors that can increase the likelihood of developing this condition. These risk factors are associated with specific genetic mutations or environmental exposures that can disrupt normal cell growth in the bone marrow.

Understanding these risk factors can help in early detection and management of Megakaryocytic Leukemia.

* Genetic factors
* Exposure to certain chemicals or radiation
* Previous chemotherapy or radiation therapy
* Inherited genetic syndromes
* Age, typically affecting older adults.

## **Diagnosis of Megakaryocytic Leukemia**

Megakaryocytic Leukemia is typically diagnosed through a series of tests and evaluations to confirm the presence of the disease. Healthcare providers may consider the patient's medical history, symptoms, and physical examination. Blood tests are commonly done to check for abnormal blood cell counts.

Additionally, bone marrow aspiration and biopsy may be performed to analyze the cells in the bone marrow. Imaging tests like X-rays or CT scans can help assess the extent of the disease. A definitive diagnosis of Megakaryocytic Leukemia is usually made based on a combination of these diagnostic procedures.

* Blood tests
* Bone marrow biopsy
* Genetic testing
* Flow cytometry
* Imaging tests (such as Xrays or CT scans)

## **Treatment for Megakaryocytic Leukemia**

Megakaryocytic Leukemia is a type of blood cancer that affects the production of platelets. Treatment options for Megakaryocytic Leukemia may include chemotherapy, targeted therapy, stem cell transplant, and immunotherapy. The specific treatment plan will depend on various factors like the patient's age, overall health, and the stage of the disease.

It's important for patients to work closely with their healthcare team to determine the best course of treatment for their individual situation. Early detection and prompt treatment can improve outcomes for patients with Megakaryocytic Leukemia.

* **Chemotherapy**: The primary treatment for Megakaryocytic Leukemia involves using powerful drugs to kill cancer cells and prevent their growth.
* **Stem Cell Transplant**: A stem cell transplant may be recommended to replace diseased bone marrow with healthy stem cells, allowing the body to produce normal blood cells.
* **Targeted Therapy**: Targeted therapy drugs specifically target cancer cells while minimizing damage to healthy cells, offering a more precise treatment approach for Megakaryocytic Leukemia.
* **Radiation Therapy**: Radiation therapy uses high energy beams to destroy cancer cells and may be used in combination with other treatments to manage Megakaryocytic Leukemia.
* **Supportive Care**: Supportive care measures such as blood transfusions, antibiotics, and managing symptoms like fatigue and infections play a crucial role in improving the quality of life for individuals with Megakaryocytic Leukemia.

## **possible Complications of Acute Megakaryoblastic Leukemia**

Acute Megakaryoblastic Leukemia (AMKL) can lead to various complications, some of which are directly related to the disease itself. In contrast, others may result from treatments or the impact of leukemia on the body. The possible complications associated with AMKL include:

* This condition can lead to bone marrow failure, where the bone marrow cannot produce enough healthy blood cells, including red blood cells, white blood cells, and platelets. This can result in anemia, increased susceptibility to infections, and bleeding tendencies
* Due to low white blood cell counts (neutropenia) caused by AMKL, patients are at a higher risk of developing infections. These infections can be bacterial, viral, or fungal and may require prompt medical intervention with antibiotics or antifungal medications
* AMKL can cause thrombocytopenia, a condition characterized by low platelet counts. This increases the risk of bleeding, manifested as easy bruising, petechiae, or prolonged bleeding from minor injuries. On the other hand, abnormal clotting may also occur in some cases
* The proliferation of abnormal cells in AMKL can lead to the enlargement of organs such as the liver, spleen, and lymph nodes (hepatosplenomegaly). This enlargement can affect organ function and may cause abdominal discomfort or pain
* In cases where there is a rapid breakdown of leukemia cells during treatment, a condition called tumor lysis syndrome may occur. This syndrome is characterized by metabolic abnormalities, such as high levels of potassium, phosphate, and uric acid in the blood, which can lead to kidney damage and other complications
* The complications of Down syndrome can include congenital heart defects, respiratory and hearing problems, thyroid conditions, and a higher risk of infections and certain types of leukemia
* Some treatments for AMKL, such as chemotherapy and radiation therapy, can increase the risk of developing secondary cancers later in life. These secondary cancers may include myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), or solid tumors

Coping with a diagnosis of Acute Megakaryoblastic Leukemia and undergoing intensive treatments can have a significant psychosocial and emotional impact on patients and their families. Supportive care, counseling, and access to mental health resources are important for addressing these aspects of the disease.

## **Prevention of Acute Megakaryoblastic Leukemia**

Preventing Acute Megakaryoblastic Leukemia (AMKL) primarily involves reducing known risk factors and focusing on general health and wellness practices. However, since AMKL can arise from genetic and environmental factors that may not be entirely preventable, the emphasis is often on early detection and prompt treatment. The key points regarding prevention include:

* Genetic counseling and testing can help assess the likelihood of developing AMKL in individuals with a family history of leukemia or genetic syndromes associated with an increased risk. This information may guide preventive measures or early detection strategies.
* Limiting exposure to known carcinogens such as benzene, ionizing radiation, and certain chemicals/environmental toxins may help reduce the risk of developing leukemia, including AMKL. This is particularly relevant for individuals working in industries or environments where such exposures are commonly noted
* Adopting/maintaining a healthy lifestyle that includes regular exercise, a balanced diet rich in fruits and vegetables, adequate hydration, and avoiding tobacco and excessive alcohol consumption can contribute to overall well-being and potentially reduce the risk of leukemia and other cancers
* Since AMKL can occur at any age and may not have specific early warning signs, regular health check-ups and screenings may aid in early detection. Blood tests, such as complete blood count (CBC), can sometimes detect abnormalities indicative of leukemia, prompting further evaluation and diagnosis
* Individuals with conditions known to predispose them to leukemia, such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN), should receive appropriate and prompt medical management with follow-up to minimize the risk of progression to AMKL or other leukemias

Research studies and clinical trials focused on leukemia prevention, risk reduction strategies, and early intervention may offer opportunities for individuals at high risk or with specific genetic profiles to explore preventive measures or targeted therapies.

## **Prognosis of Acute Megakaryoblastic Leukemia (Outcomes/Resolutions)**

The prognosis of Acute Megakaryoblastic Leukemia (AMKL) can vary widely depending on various factors, including the patient's age, overall health, the presence or absence of Down syndrome, genetic characteristics of the leukemia cells, response to treatment, and presence of complications. Some key points regarding the prognosis of AMKL include:

Overall outlook:

* AMKL is generally considered a high-risk subtype of acute myeloid leukemia (AML), particularly in children and older adults
* This condition is notably more prevalent in children with Down syndrome (DS), who experience the disease with a distinct age of onset, specific genetic changes, and generally better outcomes compared to individuals without DS
* The prognosis for AMKL has improved in recent years with advances in treatment strategies, including intensive chemotherapy regimens, stem cell transplantation, and targeted therapies

Factors influencing prognosis:

* Age at diagnosis: Young children, especially those with Down syndrome (or Trisomy 21), tend to have better outcomes compared to older adults
* Genetic mutations: Specific genetic mutations or chromosomal abnormalities, such as trisomy 21 or mutations in genes like GATA1, MPL, or JAK2, can impact the prognosis and treatment response
* Response to initial treatment: Achieving remission after induction chemotherapy and maintaining that remission through consolidation therapy are favorable indicators for prognosis
* Presence of complications: Complications such as infections, organ dysfunction, or treatment-related side effects can affect overall prognosis and treatment outcomes

**Remission and relapse:**

* Many patients with AMKL achieve remission (absence of detectable leukemia cells) following initial treatment. However, the risk of relapse remains a concern, especially in high-risk cases or those with genetic abnormalities associated with poorer outcomes
* Close monitoring during and after treatment is crucial to detect any signs of relapse early and initiate appropriate interventions

**Stem cell transplantation**: For eligible patients, especially those with high-risk features or relapsed AMKL, stem cell transplantation (bone marrow or peripheral blood stem cell transplant) may offer a chance for long-term remission or cure. The success of transplantation depends on various factors, including donor compatibility and overall health status.

**Clinical trials and novel therapies:**

* Participation in clinical trials evaluating new treatment approaches, targeted therapies, or immunotherapy strategies may provide additional options for patients with AMKL and contribute to improved outcomes
* Ongoing research and advancements in understanding the molecular mechanisms of AMKL may lead to more personalized and effective treatments in the future

Long-term follow-up care is essential for monitoring treatment response, managing potential late effects or complications, and supporting overall well-being and quality of life.

Multidisciplinary care teams, including oncologists, hematologists, supportive care specialists, and psychologists, collaborate to provide comprehensive care and support throughout the treatment journey and survivorship phase.

## **for Acute Megakaryoblastic Leukemia:**

Children with Down syndrome (Trisomy 21) have a higher risk of developing AMKL compared to the general population. Therefore, organizations like the National Down Syndrome Society often provide resources, support, and information specifically tailored to families and individuals affected by both Down syndrome and leukemia.

**Epidemiology of Acute Megakaryoblastic Leukemia (AMKL):**

* AMKL is a rare subtype of acute myeloid leukemia (AML), accounting for approximately 3–5% of all AML cases overall
* It exhibits a bimodal age distribution with peaks in young children (especially ages 1–3 years) and in adults, often between 50 and 70 years old
* In children with Down syndrome (DS-AMKL), AMKL incidence is markedly increased—occurring about 500 times more frequently than in children without Down syndrome—and is the most common form of AML in this population
* In non-Down syndrome pediatric cases (non-DS-AMKL), AMKL accounts for about 4–15% of childhood AML cases
* In adults, AMKL represents about 1–2% of AML cases and often has a poorer prognosis compared to pediatric forms
* The overall incidence is very low, with prevalence estimated at less than 1 per 1,000,000 population.
* Demographic data from the National Cancer Database (2004–2020) show an average age at diagnosis of ~40 years, median age 51 years, with a slight male predominance (~55%) and majority of cases in non-Hispanic Whites.
* Most cases are diagnosed in urban areas and treated at academic or research cancer centers.
* AMKL can arise de novo, secondary to chemotherapy, or from progression of myeloproliferative neoplasms or myelodysplastic syndromes[1](https://pmc.ncbi.nlm.nih.gov/articles/PMC2778566/).
* Children with Down syndrome-associated AMKL generally have a better prognosis and higher survival rates (~80%) compared to non-DS-AMKL and adult AMKL, which have poorer outcomes (5-year survival ~10-40%

## **Differential Diagnoses of AMKL**

Minimally Differentiated Acute Myeloid Leukemia (AML M0)

* + Lacks clear lineage differentiation morphologically.
  + Negative for myeloperoxidase (MPO) but does not express megakaryocytic markers (CD41, CD61).
  + Requires immunophenotyping to distinguish from AMKL.

Acute Panmyelosis with Myelofibrosis (APMF)

* + Aggressive AML subtype with pan myeloid proliferation and prominent marrow fibrosis.
  + Can resemble AMKL due to fibrosis and immature cells but lacks megakaryocytic marker expression.

Acute Lymphoblastic Leukemia (ALL)

* + Lymphoid lineage blasts, positive for lymphoid markers (CD19, CD3), negative for megakaryocytic markers.
  + Important to distinguish due to different treatment protocols.

Pure Erythroid Leukemia (PEL)

* + Predominance of erythroid precursors; negative for megakaryocytic markers.
  + Morphologically may overlap but immunophenotyping differentiates.

Blastic Transformation of Chronic Myeloid Leukemia (CML)

* + In a blast crisis, CML can mimic AMKL; history of CML and presence of BCR-ABL fusion gene helps differentiate.
  + Often accompanied by other myeloid lineage blasts.

Idiopathic Myelofibrosis (Primary Myelofibrosis)

* + Marrow fibrosis with atypical megakaryocytes but lacks the blast proliferation seen in AMKL.
  + Clinical courses and absence of blasts differentiate it.

Metastatic Tumors in Bone Marrow (Especially in Children)

* + Solid tumor infiltration can mimic marrow infiltration by blasts.
  + Immunohistochemistry and clinical context help exclude.

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**CHRONIC LYMPHOCYTIC LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Chronic lymphocytic leukemia (CLL) is a type of cancer of the blood and bone marrow — the spongy tissue inside bones where blood cells are made.

The term "chronic" in chronic lymphocytic leukemia comes from the fact that this leukemia typically progresses more slowly than other types of leukemia. The term "lymphocytic" in chronic lymphocytic leukemia comes from the cells affected by the disease — a group of white blood cells called lymphocytes, which help your body fight infection.

Chronic lymphocytic leukemia most commonly affects older adults. There are treatments to help control the disease.

**Causes**

Doctors aren't certain what starts the process that causes chronic lymphocytic leukemia. What's known is that something happens to cause changes (mutations) in the DNA of blood-producing cells. A cell's DNA contains the instructions that tell the cell what to do. The changes tell the blood cells to produce abnormal, ineffective lymphocytes.

Beyond being ineffective, these abnormal lymphocytes continue to live and multiply when healthy lymphocytes would die. The abnormal lymphocytes accumulate in the blood and certain organs, where they cause complications. They may crowd healthy cells out of the bone marrow and interfere with blood cell production.

Doctors and researchers are working to understand the exact mechanism that causes chronic lymphocytic leukemia.

**Risk factors**

Factors that may increase the risk of chronic lymphocytic leukemia include:

* **Your age.** This disease occurs most often in older adults.
* **Your race.** White people are more likely to develop chronic lymphocytic leukemia than are people of other races.
* **Family history of blood and bone marrow cancers.** A family history of chronic lymphocytic leukemia or other blood and bone marrow cancers may increase your risk.
* **Exposure to chemicals.** Certain herbicides and insecticides, including Agent Orange used during the Vietnam War, have been linked to an increased risk of chronic lymphocytic leukemia.
* **A condition that causes excess lymphocytes.** Monoclonal B-cell lymphocytosis (MBL) causes an increased number of one type of lymphocyte (B cells) in the blood. For a small number of people with MBL, the condition may develop into chronic lymphocytic leukemia. If you have MBL and also have a family history of chronic lymphocytic leukemia, you may have a higher risk of developing cancer.

**Symptoms of CLL**

Many people with chronic lymphocytic leukemia have no symptoms at first. Signs and symptoms might develop as the cancer progresses. They might include:

* Enlarged, but painless, lymph nodes
* Fatigue
* Fever
* Pain in the upper left portion of the abdomen, which may be caused by an enlarged spleen
* Night sweats
* Weight loss
* Frequent infections

### **When to see a doctor**

Make an appointment with your doctor if you have any persistent signs and symptoms that worry you.

**Complications of CLL**

Chronic lymphocytic leukemia may cause complications such as:

* **Frequent infections.** If you have chronic lymphocytic leukemia, you may experience frequent infections that can be serious. Sometimes infections happen because your blood doesn't have enough germ-fighting antibodies (immunoglobulins). Your doctor might recommend regular immunoglobulin infusions.
* **A switch to a more aggressive form of cancer.** A small number of people with chronic lymphocytic leukemia may develop a more aggressive form of cancer called diffuse large B-cell lymphoma. Doctors sometimes refer to this as Richter's syndrome.
* **Increased risk of other cancers.** People with chronic lymphocytic leukemia have an increased risk of other types of cancer, including skin cancer and cancers of the lung and the digestive tract.
* **Immune system problems.** A small number of people with chronic lymphocytic leukemia may develop an immune system problem that causes the disease-fighting cells of the immune system to mistakenly attack the red blood cells (autoimmune hemolytic anemia) or the platelets (autoimmune thrombocytopenia).

## 

## **Diagnosis and test**

### **Blood tests**

Tests and procedures used to diagnose chronic lymphocytic leukemia include blood tests designed to:

* **Count the number of cells in a blood sample.** A complete blood count may be used to count the number of lymphocytes in a blood sample. A high number of B cells, one type of lymphocyte, may indicate chronic lymphocytic leukemia.
* **Determine the type of lymphocytes involved.** A test called flow cytometry for immunophenotyping helps determine whether an increased number of lymphocytes is due to chronic lymphocytic leukemia, a different blood disorder or your body's reaction to another process, such as infection.  
  If chronic lymphocytic leukemia is present, flow cytometry may also help analyze the leukemia cells for characteristics that help predict how aggressive the cells are.
* **Analyze lymphocytes for genetic changes.** A test called fluorescence in situ hybridization (FISH) examines the chromosomes inside the cancerous lymphocytes to look for changes. Doctors sometimes use this information to determine your prognosis and help choose a treatment.

### **Other tests**

In some cases, your doctor may order additional tests and procedures to aid in diagnosis, such as:

* Tests of your leukemia cells that look for characteristics that could affect your prognosis
* Bone marrow biopsy and aspiration
* Imaging tests, such as computerized tomography (CT) and positron emission tomography (PET)

### **Staging**

Once a diagnosis is confirmed, your doctor uses the information about your cancer to determine the stage of your chronic lymphocytic leukemia. The stage tells your doctor how aggressive your cancer is and how likely it is to get worse quickly.

Chronic lymphocytic leukemia stages can use letters or numbers. In general, the earliest stages of disease don't need to be treated right away. People with cancer in the later stages may consider beginning treatment immediately.

**Treatment**

Your treatment options for chronic lymphocytic leukemia depend on several factors, such as the stage of your cancer, whether you're experiencing signs and symptoms, your overall health, and your preferences.

### **Treatment may not be needed right away**

If your chronic lymphocytic leukemia doesn't cause symptoms and doesn't show signs of getting worse, you may not need treatment right away. Studies have shown that early treatment doesn't extend lives for people with early-stage chronic lymphocytic leukemia.

Rather than put you through the potential side effects and complications of treatment before you need it, doctors carefully monitor your condition and reserve treatment for when your leukemia progresses.

Your doctor will plan a checkup schedule for you. You may meet with your doctor and have your blood tested every few months to monitor your condition.

### **Treatments for intermediate and advanced stages**

If your doctor determines that your chronic lymphocytic leukemia requires treatment, your options may include:

* **Chemotherapy.** Chemotherapy is a drug treatment that kills quickly growing cells, including cancer cells. Chemotherapy treatments can be administered through a vein or taken in pill form. Depending on your situation, your doctor may use a single chemotherapy drug or you may receive a combination of drugs.
* **Targeted drug therapy.** Targeted drug treatments focus on specific abnormalities present within cancer cells. By blocking these abnormalities, targeted drug treatments can cause cancer cells to die.
* **Immunotherapy.** Immunotherapy uses your immune system to fight cancer. Your body's disease-fighting immune system may not attack your cancer because the cancer cells produce proteins that help them hide from the immune system cells. Immunotherapy works by interfering with that process.
* **Bone marrow transplant.** A bone marrow transplant, also known as a stem cell transplant, uses strong chemotherapy drugs to kill the stem cells in your bone marrow that are creating diseased lymphocytes. Then healthy adult blood stem cells from a donor are infused into your blood, where they travel to your bone marrow and begin making healthy blood cells.  
  As new and more-effective drug combinations have been developed, bone marrow transplant has become less common in treating chronic lymphocytic leukemia. Still, in certain situations this may be a treatment option.

Treatments may be used alone or in combination with each other.

**Alternative medicine**

No alternative treatments have been proved to cure chronic lymphocytic leukemia.

### **Alternative treatments for coping with fatigue**

Some alternative medicine therapies may help you cope with fatigue, which is commonly experienced by people with chronic lymphocytic leukemia. Your doctor can treat fatigue by controlling the underlying causes, but often medications alone aren't enough. You may find relief through alternative therapies, such as:

* Acupuncture
* Exercise
* Massage
* Yoga

Talk to your doctor about your options. Together you can devise a plan to help you cope with fatigue.

**DIFFERENTIAL DIAGNOSIS**

* Acute Lymphoblastic Leukemia (ALL)
* Acute promyelocytic leukemia
* Diffuse large cell lymphoma
* Follicular lymphoma
* Hairy cell leukemia
* Lymphoblastic lymphoma
* Mantle cell lymphoma
* Non-Hodgkin lymphoma
* Monoclonal B-cell lymphocytosis (MBL)
* Prolymphocytic lymphoma (PLL)
* Lymphoplasmacytic lymphoma
* Histologic transformation — CLL/SLL can convert to more aggressive histology (Richter transformation), either diffuse large B cell lymphoma or Hodgkin lymphoma.

**EPIDEMIOLOGY**

CLL comprises 25 to 30% of total leukemias in the United States. According to the American Cancer Society, there will be approximately 21,040 new CLL cases and about 4,060 deaths in the year of 2020. Worldwide, 191,000 cases and 61,000 deaths are attributed to CLL/SLL every year. CLL can affect adults as young as 30 years of age. However, it is mostly seen in adults with an average age of 70 years. CLL is extremely rare in children. The incidence is known to rapidly increase with increasing age. CLL has a slightly higher incidence in male populations than female populations (1.3 to 1 to 1.7 to 1). However, studies have shown that women can have a more aggressive form of the disease than men.

The incidence of CLL varies by geographic location and race. CLL is most commonly seen in adults of the Western population. It is high amongst the Caucasian population compared to the Asian Pacific Islanders or the African-American population. The incidence of CLL in Western countries is similar to that of the United States but is rarely seen in Asian countries (China and Japan). CLL is common amongst the Jews of Eastern European descent. It is most commonly seen in Non-Hispanic Whites and least common in Asians. The incidence in African Americans is in between the Caucasian and the Asian ethnicity groups.

CLL is reported to have a genetic basis and is known to run in families (familial CLL). The age at diagnosis of the second-generation offspring is nearly 20 years younger as compared to the parent. First-degree relatives (siblings, children, or parents) of CLL patients have double the risk for CLL. Moreover, 17% of first-degree family members of CLL patients had monoclonal B cell lymphocytosis, which is a precursor of CLL. Ultimately only a small percentage of patients with monoclonal B-cell lymphocytosis (MBL) will develop into CLL.

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### **CHRONIC MYELOID LEUKEMIA (CML)**

**Definition and description**

Chronic myeloid leukemia (CML) is blood cancer that starts in the blood-forming myeloid cells or stem cells in your bone marrow. The condition has other names: chronic myelogenous leukemia or chronic granulocytic leukemia. Many people with CML may have normal life spans, thanks to therapy that has turned the condition from a life-threatening illness into a chronic illness that medication can manage.

#### **How fast does CML progress or get worse?**

It takes a long time for CML to get worse. You can have this condition for years before noticing symptoms. Many people learn they have CML after routine blood test results show unusual blood cell counts. Prompt treatment keeps CML from getting worse. Without treatment, chronic myeloid leukemia can become a life-threatening illness within three to four years.

## **Symptoms and Causes**

You can have CML without having noticeable symptoms. Chronic myeloid leukemia symptoms are mild and get worse over time. Common CML symptoms may include:

* Fatigue or weakness.
* Shortness of breath (dyspnea).
* Fever.
* Night sweats.
* Unexplained weight loss.
* Abdominal swelling or discomfort in the upper left part of your belly, where you can find your spleen.
* Feeling full when you haven’t eaten much.

### **What causes chronic myeloid leukemia?**

People with CML have an acquired genetic mutation or change in myeloid stem cells growing in their bone marrow. Acquired mutations aren’t present at birth and aren’t something you can inherit. Acquired mutations happen during your lifetime.

In genetic mutations, mutated or changed genes give cells new instructions on what to do. In this case, the mutation creates a new fused gene, *BCR-ABL*. The new gene triggers the following chain of events that lead to chronic myeloid leukemia:

* The *BCR-ABL* gene gives new instructions to myeloid stem cells.
* The stem cells make an abnormal version of tyrosine kinase enzymes.
* These enzymes help manage cell growth. They act like “on” and “off” switches.
* The abnormal tyrosine kinase enzymes don’t have an “off” switch.
* Without an “off” switch, myeloid stem cells in your bone marrow divide and multiply uncontrollably.
* Over time, abnormal myeloid stem cells in your bone marrow start dividing and multiplying uncontrollably, making unusually large amounts of immature white blood cells (blasts).
* Eventually, the blasts accumulate in your bone marrow, making it hard for your bone marrow to make normal red blood cells, white blood cells and platelets. You may have fewer red blood cells but more platelets and abnormal white blood cells.

#### **Risk factors for CML**

The only risk factor for CML is exposure to high levels of radiation — and this applies to very few people.

#### **Complications of CML**

People with CML may develop:

* Anemia. This condition happens when you don’t have enough red blood cells.
* Enlarged spleen (splenomegaly).

#### **Can CML lead to other types of cancer?**

Yes, it can. People with CML may have an increased risk of other types of cancer (second cancers). A recent study showed about 30% of people with chronic myeloid leukemia developed second cancers, including:

* Small intestine cancer.
* Thyroid cancer.
* Stomach cancer.
* Lung cancer.
* Prostate cancer.

## **Diagnosis and Test**

Healthcare providers may suspect you have CML if you have unusual blood test results. But they actually diagnose CML with chromosome or genetic tests that identify genetic changes or mutations. Common tests for CML include:

* Complete blood count (CBC): Providers may check for high levels of white blood cells or low red blood cell levels.
* Bone marrow aspiration or bone marrow biopsy: Providers take small samples of fluid or tissue for genetic tests. A medical pathologist will perform tests to analyze abnormal cells’ genetic makeup.
* Computed tomography (CT) scan: Providers use this test to determine if CML is affecting other parts of your body.
* Ultrasound: Providers may do this test to determine if your spleen is larger than normal. An enlarged spleen is a CML symptom.

#### **What are CML stages?**

Unlike many types of cancer, healthcare providers don’t characterize chronic myeloid leukemia by cancer stages. They characterize CML as being in one of four phases:

* Chronic CML:The term “chronic” often means you have a long-term condition. In CML, the term refers to the percentage of blasts (immature white blood cells) in your bone marrow and blood. In chronic CML, blasts make up about 10% of cells in your blood and bone marrow. Between 80% and 90% of people diagnosed with the condition have chronic CML. Some but not all people with chronic CML have symptoms.
* Accelerated CML:In this phase, blasts make up 10% to 19% of cells in your blood or bone marrow. Providers may also look for basophils. Basophils are white blood cells that release enzymes to improve blood flow and prevent blood clots. If you have CML, you may have increased basophil levels.
* Blast (blast crisis) CML:Blast CML can be life-threatening. In blast CML, tests show blasts make up 20% or more of cells in your bone marrow or blood. Most people with blast phase CML have very noticeable symptoms such as extreme fatigue, fever, weight loss and shortness of breath.
* Resistant CML: CML that comes back after treatment or doesn’t respond to treatment is called resistant CML.

## **Management and Treatment**

Healthcare providers typically treat chronic phase CML with tyrosine kinase inhibitors (TKIs). TKIs are a type of targeted therapy. In CML, the targets are the abnormal *BCR-ABL* enzymes that let abnormal white blood cells divide and multiply uncontrollably. TKIs block the enzymes so that CML cells start to die.

TKIs have made a huge difference for people with chronic myeloid leukemia. Before TKIs, only about 20% of people with the condition were alive five years after diagnosis. TKIs changed that outcome for people with early (chronic) CML.

TKIs put chronic myeloid leukemia into remission. (Remission means you don’t have CML symptoms and tests don’t find signs of the disease.) Most people take TKIs for the rest of their lives. However, recent studies show CML remains in remission even after people stop taking TKIs. This is treatment-free remission. Common TKIs to treat chronic phase CML include:

* Imatinib (Gleevec®).
* Dasatinib (Sprycel®).
* Nilotinib (Tasigna®).
* Bosutinib (Bosulif®).
* Ponatinib (Iclusig®).
* Asciminib (Scemblix®).

#### **What are TKI side effects?**

Side effects vary based on the specific TKI but may include:

* Stomach pain.
* Fatigue.
* Diarrhea.
* Muscle cramps.
* Edema.
* Pleural effusion (fluid accumulation around your lungs).
* Pancreatitis.
* Damage to your liver.
* Lower-than-normal white blood cell and platelet counts.

#### **What are other CML treatments?**

If TKIs aren’t effective, providers may use chemotherapy along with or instead of a TKI.

## **Outlook / Prognosis**

That depends on your situation. If treatment puts chronic myeloid leukemia into remission, you won’t have symptoms or signs of disease, but you’ll need medication to keep CML in remission. Most people with CML attend frequent, routine appointments to see how well their treatment is working.

#### **What about treatment-free remission?**

Treatment-free remission (TFR) means you don’t have CML symptoms or signs even after you stop taking a TKI. Recent studies show about 40% of people who stop treatment remain in remission for several years. But TFR is a relatively recent approach to treating chronic myeloid leukemia. Not everyone is a candidate. If you have chronic myeloid leukemia, it’s important that you talk to your provider before stopping treatment.

#### **Is CML curable?**

Right now, allogeneic stem cell transplantation is the only way to “cure” chronic myeloid leukemia. Allogeneic stem cell transplantation uses donated stem cells. It’s a complicated medical treatment. Its side effects are more serious than targeted therapy side effects. For that reason, providers typically only use stem cell transplantation to treat resistant CML.

##### **CML survival rate**

When you think about survival rates, it’s important to remember that survival rates can’t predict how long you’ll live. Survival rates are based on other peoples’ experiences. What was true for them may not be true for you.

That being said, overall, 90% of people with CML are alive five years after diagnosis. (Before TKI, only 22% of people with CML were alive at the five-year mark.) If you have CML, your healthcare provider is your best resource for information about what you can expect.

## **Prevention**

No, it can’t. Medical researchers know CML happens when a specific gene mutates, but they haven’t discovered why that mutation happens.

## **Living With**

If you have chronic myeloid leukemia, you may need to take medication for the rest of your life. You’ll also need regular checkups so your healthcare provider can monitor your overall health. They’ll look for signs that CML has come back and for signs of second cancers.

#### **When to see a doctor**

In general, you should expect to see your provider every few months for the rest of your life

## **Epidemiology**

The American Cancer Society (ACS) estimates that 9280 new cases of CML will be diagnosed in 2024, 5330 in males and 3950 in females. The ACS estimates that 1280 deaths from CML will occur in 2024, 750 in males and 530 in females.

The incidence of new CML cases rose on average 1.2% each year over 2012–2021, reaching 2.0 per 100,000 population in 2022. Age-adjusted death rates remained stable over 2013–2022, at 0.3 per 100,000 population per year.

CML is most often diagnosed in people aged 65-74 years. Median age at diagnosis is 66 years. CML is more common in males than in females: incidence rates per 100,000 population are 2.5 in males versus 1.5 in females.

**DIFFERENTIAL DIAGNOSIS**

## Main Differential Diagnosis of CML

## **Leukemoid Reaction**

* + Reactive increase in white blood cells due to infection or inflammation.
  + Unlike CML, leukemoid reaction usually has a high leukocyte alkaline phosphatase (LAP) score, no Philadelphia chromosome (Ph), and no BCR-ABL fusion gene.
  + Basophilia and eosinophilia are uncommon in leukemoid reactions.

Chronic Neutrophilic Leukemia (CNL)

* + Characterized by persistent neutrophilia without the Ph chromosome.
  + Basophils and eosinophils are typically normal, unlike in CML.
  + Mutations in CSF3R gene are often present.

Atypical Chronic Myeloid Leukemia (aCML)

* + BCR-ABL1 negative.
  + Features include leukocytosis with dysplastic neutrophils and increased immature granulocytes.
  + Lacks the Ph chromosome and BCR-ABL fusion.

Chronic Myelomonocytic Leukemia (CMML)

* + Features monocytosis (>1 x 10^9/L) with dysplastic features.
  + No Ph chromosome or BCR-ABL fusion gene.

Acute Myeloid Leukemia (AML)

* + Presence of >20% blasts in blood or bone marrow.
  + No Ph chromosome in all myeloid cells except in rare cases of Ph-positive AML.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

* + Ph chromosome present but confined to lymphoblasts, not all myeloid cells.
  + Rapid onset and different clinical courses from CML.

Other Myeloproliferative Neoplasms (MPNs)

* + Polycythemia Vera (PV): Elevated red cell mass, often with JAK2 mutation.
  + Essential Thrombocythemia (ET): Elevated platelets, JAK2 or CALR mutations.
  + Primary Myelofibrosis (PMF): Bone marrow fibrosis, anemia, splenomegaly.

Myelodysplastic Syndromes (MDS)

* + Cytopenias with dysplastic marrow features, no Ph chromosome.

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## **Chronic Myelomonocytic Leukemia (CMML)**

**Definition and description**

Chronic myelomonocytic leukemia (CMML) is a rare type of blood cancer. Having blood cancer means that there’s a problem with how your bone marrow — the spongy tissue inside your bones — makes blood cells. With CMML, your bone marrow makes too many abnormal monocytes, a type of white blood cell. These cells can crowd out cells you need, like red blood cells, platelets and healthy white blood cells.

Doctors classify this condition as a myeloproliferative neoplasm/myelodysplastic syndrome (MPN/MDS). Here’s what this means:

* Myeloproliferative neoplasm (MPN). Your bone marrow makes *too many* blood cells. Too many of one type of blood cell can cause problems with how your blood works.
* Myelodysplastic syndrome (MDS). Your bone marrow makes *abnormal* blood cells. Instead of having mature, healthy blood cells, you may have too many immature blast cells.

CMML can range on a spectrum from slow-growing to aggressive. Your healthcare provider will explain potential treatment options that may slow its progression.

## **Symptoms and Causes**

CMML doesn’t always cause symptoms. The first sign of chronic myelomonocytic leukemia may be abnormal results on a blood test. When symptoms are noticeable, they usually develop gradually. CMML symptoms include:

* Fatigue or weakness (a sign of low red blood cells, or anemia)
* Frequent infections (a sign of low white blood cells, or neutropenia)
* Excessive nosebleeds or bruising easily (a sign of low platelets, or thrombocytopenia)
* Enlarged spleen (splenomegaly)
* Enlarged liver (hepatomegaly)
* Unexplained weight loss
* Night sweats
* Bone pain
* Fever

### **Chronic myelomonocytic leukemia causes**

Researchers don’t know what causes CMML. But they have identified several gene changes (mutations) associated with this condition. If you’re diagnosed, you’ll likely have more than one mutation. Some of the most common ones involve the following genes (with the most common listed first):

* *TET2*
* *SRSF2*
* *ASXL1*
* *RAS*

#### **Risk factors**

Risk factors for chronic myelomonocytic leukemia include:

* Age. Your risk increases as you get older. The median age of diagnosis is between 73 and 75. A median is a midpoint. This means half of people diagnosed are younger, and half are older.
* Sex. More males are diagnosed than females.
* Cancer treatment. About 1 in 10 people who develop CMML had previous cancer treatments like chemotherapy and radiation. Healthcare providers consider the risk of future cancers when they prescribe these treatments. They only suggest them when the benefits clearly outweigh the risks.

### **Complications of CMML**

In about 2 out of 10 cases, chronic myelomonocytic leukemia transforms into acute myeloid leukemia (AML). Ask your healthcare provider about your risk of developing AML based on your diagnosis and risk factors.

## **Diagnosis and Tests**

Your healthcare provider will consider your symptoms and ask about your medical history. They’ll perform tests to check your blood cells. Tests may include:

* Complete blood count. A monocyte count that’s too high (monocytosis) may be a sign of CMML.
* Peripheral blood smear. Monocytes that look irregular or immature (blast cells) when viewed beneath a microscope may be a sign of CMML.
* Bone marrow biopsy. Your provider may need to take a sample of bone marrow and test it in a lab to check for abnormal monocytes.
* Genetic testing. Providers also check for gene mutations associated with other blood cancers. This can help them eliminate other conditions that involve similar symptoms and blood test results.

#### **Staging**

Healthcare providers determine how advanced CMML is (cancer staging) based on how many blast cells you have. The stages are:

* CMML-1. Less than 4 out of every 100 cells in your blood are blasts. Less than 9 out of every 100 cells in your bone marrow are blasts.
* CMML-2. Five to 19 out of every 100 cells in your blood are blasts. Ten to 19 out of every 100 cells in your bone marrow are blasts.

The stage helps your provider decide the most effective treatment.

## **Management and Treatment**

First, you may need treatment to ensure you have enough healthy blood cells. You may need medications or regular blood transfusions to boost your blood cell counts. This may be a part of palliative care to help you manage symptoms.

Other treatments that target CMML directly include:

* Allogeneic stem cell transplant. This is the only treatment that can potentially cure CMML. But it’s not an option for most people. Also, it can cause life-threatening complications like graft vs. host disease.
* Chemotherapy. Chemo makes it harder for the monocytes to multiply out of control. This can provide symptom relief. Drug types include hydroxyurea and hypomethylating agents (HMA).
* Clinical trials. Your provider may recommend taking part in a clinical trial if other treatments aren’t helping. Current clinical trials are studying the effectiveness of newer CMML treatments. These include targeted therapy and immunotherapy.

### **When to see a doctor**

You’ll see your healthcare provider regularly (usually every one to six months). It’s important not to skip appointments. During these visits, your provider will ask about your symptoms and run blood tests. They’ll assess how your treatment is working and make adjustments as needed.

In the meantime, contact your provider if you’re experiencing unexpected or severe treatment side effects. Your provider will let you know what signs to look out for based on the treatment you’re getting.

## **Outlook / Prognosis**

The median life expectancy for people diagnosed with CMML is approximately between one to three years. Again, a “median” is a midpoint. This means that half of people have a shorter lifespan and half live longer. But lots of factors shape your likely outcome, or prognosis. These include:

* Blood test results. Your blood cell counts provide clues about your prognosis. Important values include your monocyte, blast cell and platelet counts. Your hemoglobin level is another important number that your healthcare provider will monitor.
* Genetic mutations. Some mutations, like mutations in the *ASXL1* gene, are associated with a worse prognosis.
* Frequency of blood transfusions. Your outcome is generally better if you don’t need repeat blood transfusions to restore your blood cells.

Your prognosis also depends on whether your condition progresses to AML. This is more likely to happen if you have CMML-2.

### **Is there anything I can do to feel better?**

One of the best things you can do if you have CMML is to take charge of your health in every way you can. Right now, eating nutrient-rich foods and getting enough sleep are essential. Balancing activity and rest are important, too. Connecting with others living with cancer is a good way to combat feelings of isolation that can come up. Speak to a therapist with expertise in working with people diagnosed with cancer.

Cancer can make a person feel helpless, but know that you’re still in charge of your life. And there are treatments available to help.

# **Key Statistics About Chronic Myelomonocytic Leukemia (CMML)**

Chronic myelomonocytic leukemia (CMML) is rare. About 1 or 2 out of every 100,000 people develop CMML each year.

* This disease occurs most often in older people, and it’s very rare in young people.
* Most people diagnosed with CMML are aged 65 years or older.
* CMML occurs more often in men than in women.

## **Research into the genetics﻿ of CMML**

Researchers﻿ are learning more about which changes (mutations) in the DNA inside normal bone marrow cells can cause them to develop into leukemia cells. (DNA is the substance that makes up our genes.)

Studies have found that changes in certain genes in CMML cells may help predict a person's outcome and how likely they are to go on to develop acute leukemia.

Researchers also hope that finding some of the gene changes in CMML cells might lead to treatments that target these changes (see below).

## **Research into treating CMML with chemotherapy and other drugs**

Studies are being done to find which chemotherapy drugs can best treat CMML, while trying to limit side effects. New drugs are being developed and tested.

As researchers have learned more about what makes cancer cells different from normal cells, they've developed drugs that target these differences. Studies are now looking at some of these targeted therapies to treat CMML. These drugs target things like specific cell signaling pathways to shut down CMML cell growth.

## **Research into treating CMML with a stem cell transplant**

A stem cell transplant is one of the main types of treatment for CMML, if it can be done. Scientists continue to refine stem cell transplants so that they work better and cause fewer problems. They are also looking at which patients will benefit the most and how newer transplant methods might be used to treat CMML.

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**HAIRY CELL LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Hairy cell leukemia is a cancer of the white blood cells. The white blood cells help fight off germs. There are a few different types of white blood cells. The white blood cells involved in hairy cell leukemia are called B cells. B cells are also called B lymphocytes.

In hairy cell leukemia, the body makes too many B cells. The cells don't look like healthy B cells. Instead, they've undergone changes to become leukemia cells. The leukemia cells look "hairy" under a microscope.

Hairy cell leukemia cells keep living when healthy cells would die as part of the natural cell life cycle. The leukemia cells build up in the body and cause symptoms.

Hairy cell leukemia often gets worse slowly. Treatment might not need to start right away. When it's needed, treatment is usually with chemotherapy.

Scientists found a type of cancer that looks like hairy cell leukemia, but it gets worse much faster. This other type of cancer is called hairy cell leukemia variant. It's considered a separate type of cancer from hairy cell leukemia, even though it has a similar name.

**Causes**

It's not clear what causes hairy cell leukemia.

Hairy cell leukemia begins in the white blood cells. The white blood cells help fight germs in the body. There are a few types of white blood cells. The white blood cells involved in hairy cell leukemia are called B cells.

Hairy cell leukemia happens when B cells develop changes in their DNA. A cell's DNA contains the instructions that tell a cell what to do. The changes tell the B cells to make a lot more B cells that don't work right. These cells go on living when healthy cells would die as part of the natural cell life cycle.

The B cells that don't work right crowd out healthy blood cells in the bone marrow and other organs. This leads to the symptoms and complications of hairy cell leukemia. For example, the extra cells can cause swelling in the spleen, liver and lymph nodes. If there isn't enough room for healthy blood cells, this can lead to frequent infections, easy bruising and feeling very tired.

**Risk factors**

The risk of hairy cell leukemia may be higher in:

* **Older adults.** Hairy cell leukemia can happen at any age. But most people diagnosed with hairy cell leukemia are in their 50s or 60s. It's rare in children.
* **Males.** Hairy cell leukemia can happen to anyone. But it's more likely in males.

**Symptoms**

Hairy cell leukemia might not cause symptoms. Sometimes a health care provider finds it by accident during a blood test for another condition.

When it causes symptoms, hairy cell leukemia might cause:

## A feeling of fullness in your belly that may make it uncomfortable to eat more than a little at a time

## Fatigue

## Easy bruising

## Recurring infections

## Weakness

## Losing weight without trying

### **When to see a doctor**

## Make an appointment with your health care provider if you have any persistent signs and symptoms that worry you.

## **DIAGNOSIS AND TEST**

## To diagnose hairy cell leukemia, your health care provider may recommend:

## Physical exam. Your provider may feel your spleen to see if it's too big. The spleen is an oval-shaped organ on the left side of the upper abdomen. If your spleen is too big you might feel a fullness in your belly. You might have pain or discomfort when you eat.

## Blood tests. You might have a blood test to measure the levels of blood cells in your blood. This test is called a complete blood count (CBC) with differential. You have three main types of blood cells in your blood. They include red blood cells, white blood cells and platelets. In hairy cell leukemia, a CBC test may show all levels of these cells are too low. Another type of blood test might involve looking at your blood under the microscope. This test can find hairy cell leukemia cells. This test is called a peripheral blood smear.

## Bone marrow biopsy. A bone marrow biopsy is a procedure to remove some of your bone marrow for testing. Your provider will remove a small amount of bone marrow from your hip area. This sample is used to look for hairy cell leukemia cells.

## Lab tests to analyze the leukemia cells. Hairy cell leukemia cells collected from your blood and bone marrow are tested in a lab. These tests look at the changes in the cells' DNA. This helps your provider understand your prognosis and what treatments are best for you.

## Computerized tomography (CT) scan. A CT scan shows detailed images of the inside of your body. Your provider may order a CT scan to look for swelling in your spleen and your lymph nodes.

## 

## **Treatment**

## Hairy cell leukemia treatments are good at controlling the disease. But they can't make it go away completely. Instead, treatments can control the cancer so that you can go about your life as usual. People with hairy cell leukemia can live with the disease for many years.

### Treatment might not need to start right away

## Treatment for hairy cell leukemia doesn't always need to start right away. This cancer often gets worse very slowly over time. You might choose to wait and have treatment if the cancer starts to cause symptoms.

## If you don't have treatment, you'll have regular appointments with your health care provider. You might have blood tests to see if hairy cell leukemia is getting worse.

## You might decide to start treatment if you start to get hairy cell leukemia symptoms. Most people with hairy cell leukemia will eventually need treatment.

### **Chemotherapy**

## Chemotherapy is a drug treatment that uses powerful drugs to kill cancer cells. It's often the first treatment for hairy cell leukemia. Chemotherapy is very effective for hairy cell leukemia. Most people get a complete or partial remission after chemotherapy. Remission means you have no signs of cancer.

## Chemotherapy for hairy cell leukemia can be given as a shot. Or it can be given as an infusion into a vein.

## If your hairy cell leukemia comes back, your provider might recommend repeating chemotherapy with the same drug or trying a different drug. Another option may be targeted drug therapy.

### **Targeted drug therapy**

## Targeted drug treatments attack specific chemicals present within cancer cells. By blocking these chemicals, targeted drug treatments can cause cancer cells to die.

## Targeted drug therapy is sometimes used as a first treatment for hairy cell leukemia. It can be used with chemotherapy. More often, targeted therapy is an option if the cancer comes back after chemotherapy.

## Your health care provider will have your cancer cells tested to see whether targeted drug therapy is likely to work for you.

## **Alternative medicine**

## No alternative medicines are helpful for treating hairy cell leukemia. Alternative medicine might be helpful in other ways. It may help you cope with the stress of a cancer diagnosis and the treatment side effects.

## Talk to your health care provider about your options, such as:

## Art therapy

## Exercise

## Meditation

## Music therapy

## Relaxation exercises

## Spirituality

## 

## **Complications**

Hairy cell leukemia often gets worse very slowly. Sometimes it stays stable for many years. For this reason, few complications of the disease occur.

### **Too few healthy blood cells**

If there are too many leukemia cells in the body, they can crowd out the healthy blood cells. That can lead to:

* **Infections.** Your body needs healthy white blood cells to fight off germs. If your body can't make enough healthy white blood cells, you might get more infections.
* **Bleeding.** Your body needs healthy platelet cells to control bleeding. If the number of platelets in your blood is low, you might notice that you bruise more easily. You might also have bleeding from the nose or gums.
* **Anemia.** Your body needs healthy red blood cells to carry oxygen through your body. Having too few red blood cells is called anemia. Anemia can make you feel very tired.

### **Increased risk of other cancers**

Some studies found that people with hairy cell leukemia have an increased risk of other types of cancer. The other cancers include non-Hodgkin's lymphoma, Hodgkin's lymphoma and others. It's not clear if the other cancers are caused by hairy cell leukemia or by cancer treatments.

**EPIDEMIOLOGY**

Hairy cell leukemia accounts for less than 2% of all leukemias. Its incidence is 0.3 cases per 100,000 individuals with an average male-to-female ratio of 1.5-2:1 and median age at diagnosis of 58 years. The incidence is approximately three times higher in White than in Black populations. HCL-v is estimated to be 0.2 cases per 100,000. HCL-v affects mainly elderly patients with a median age of 71 years.

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**MAST CELL LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Mast cell leukemia (MCL) is a quick-progressing condition that leads to the buildup of mast cells in your bone marrow and other tissues. It falls into a group of diseases collectively known as systemic mastocytosis.

Systemic mastocytosis is rare and only affects about 13 out of 100,000 people. MCL is the rarest form of systemic mastocytosis, making up less than 1 percent of cases.

MCL can cause a variety of symptoms including low blood pressure, rashes, and itchy skin. It tends to have a poor outlook due to its rarity and lack of research on the best way to treat it.

Keep reading to learn everything you need to know about MCL, including how it differs from other types of leukemia and the latest treatment options.

## **mast cell leukemia**

MCL is an extremely rare condition that falls into a group of diseases known as systemic mastocytosis. Mastocytosis is a group of conditions characterized by the abnormal growth and buildup of a type of white blood cell called mast cells in your bodily tissues.

### **mast cells**

Mast cells are a type of white blood cell produced by your bone marrow. One of their primary functions is to release histamines and other chemicals to help fight infections. These chemicals also produce many classic allergy symptoms like excess mucus, itchiness, and swelling.

Mastocytosis can be divided into two types:

* Cutaneous mastocytosis. This is when large numbers of mast cells gather in your skin but not in other parts of your body. It’s most common in children.
* Systemic mastocytosis. This happens when mast cells gather in tissues like your skin, organs, and bones. This is the category that MCL falls into.

## **Causes of mast cell leukemia**

All the blood cells in your body start off as hematopoietic stem cells, also known as blood stem cells. They’re found in your bone marrow. These stem cells become one of two types of cells:

* myeloid progenitor cells
* lymphoid progenitor cells

Leukemia is a group of cancers that’s caused by cells in your bone marrow that produce abnormal or underdeveloped blood cells. Leukemias are classified based on the type of cells that are affected.

MCL is one of several types of leukemia that are caused by the abnormal growth of cells from myeloid progenitor cells. Myeloid progenitor cells can become mast cells, platelets, red blood cells, and white blood cells.

In people with MCL, at least 20 percent of mast cells in your bone marrow or 10 percent of the mast cells in your blood are abnormal. The buildup of these cells can lead to organ dysfunction that can affect your bone marrow, liver, or spleen.

It’s not entirely clear why MCL develops, but several gene mutations in the *KIT* gene are linked to the development of MCL. In about 15 percent of cases, MCL develops from a pre-existing mast cell disease.

## **Symptoms of mast cell leukemia**

The following are symptoms among patients with mast cell leukemia may experience:

* lethargy and weakness
* fainting
* flushing
* fever
* fast heart beat (tachycardia)
* losing more than 10 percent of body weight
* diarrhea
* nausea and vomiting
* loss of appetite
* itchy skin blisters
* bone pain

## **Diagnosis and test**

MCL most commonly occurs in adults. Half of people with MCL are over age 52, but some as young as 5 years old have been described in the medical literature.

A diagnosis for mast cell leukemia requires you to:

* meet the criteria for systemic mastocytosis
* show signs of organ damage
* have at least 20 percent atypical mast cells in your bone marrow or ten percent in your blood

For a systemic mastocytosis diagnosis, the World Health Organization’s criteria require you to meet the major criterion or at least three minor criteria.

#### **Major criterion**

* clusters of at least 15 mast cells in bone marrow biopsies

#### **Minor criteria**

* more than 25 percent of mast cells are atypical measure in bone marrow
* *KIT* gene mutation at codon 816 in bone marrow or other internal organs
* mast cells exhibit CD2 or CD25
* baseline serum tryptase level greater than 20 ng/mL

To diagnose systemic mastocytosis and MCL, an oncologist will likely order a bone marrow biopsy. This is when a small tissue sample is taken with a long needle, often from your hip bone. The doctor may also take a biopsy of other affected organs.

Medical professionals can use your biopsy sample to look for certain genes that are common in people with MCL. They’ll run tests to assess the density and appearance of your mast cells.

A blood test may be ordered to search for markers of MCL like:

* low red blood cell count
* high histamine levels
* low platelet levels
* high white blood cell count
* low albumin levels
* high tryptase level

**Treatment**

There’s no standard therapy for MCL due to the rarity of the disease and lack of research. Also, no one particular treatment has shown consistently effective results.

Treatment may include medications known as monoclonal antibodies, tyrosine kinase inhibitors, and forms of chemotherapy used to treat acute myeloid leukemia.

Allogeneic bone marrow transplants are also sometimes needed. This procedure involves transplanted bone marrow stem cells from a donor to replace cells damaged by chemotherapy.

## **outlook for people with MCL**

The outlook for MCL is generally poor. About half of people who develop MCL live less than 6 months from the time of diagnosis. MCL often leads to multiorgan failure or anaphylactic shock due to the buildup of mast cells.

Despite the poor prognosis, some people have a better result. The man in the 2017 case study went into full remission after receiving treatment, and some people’s disease progresses slower than predicted.

### **Staying hopeful**

The diagnosis and treatment process for leukemia can be overwhelming for anyone. However, it’s important to remember that you are not alone and new treatments are being studied.

As researchers continue to learn about MCL, treatment will likely become more refined in the future, and it’s possible the outlook of the disease will improve.

**DIFFERENTIAL DIAGNOSIS**

## Myelomastocytic Leukemia (MML)

* A rare myeloid neoplasm characterized by increased immature mast cells/metachromatic blasts (≥10%) in bone marrow, usually in the context of advanced myeloid neoplasms such as AML or MDS.
* Distinguishing features:
  + MML lacks systemic mastocytosis (SM) diagnostic criteria (no compact mast cell aggregates).
  + Mast cells in MML are CD25-negative and typically lack KIT mutations.
  + MCL mast cells are CD25-positive and usually harbor KIT mutations (especially D816V).
  + MCL requires ≥20% atypical/immature mast cells in marrow; MML requires ≥10%.
* MML is considered a distinct entity and may be underdiagnosed without routine tryptase and CD117 staining.

Aggressive Systemic Mastocytosis (ASM)

* A form of systemic mastocytosis with organ damage but <20% mast cells in marrow.
* MCL is considered a leukemic variant of SM with ≥20% mast cells in marrow.
* ASM and MCL share KIT mutations and CD25 positivity but differ in mast cell burden and clinical aggressiveness.

Acute Basophilic Leukemia (ABL)

* Characterized by blasts with basophilic granules that may express tryptase and CD25 but typically lack CD117 expression.
* Serum tryptase levels are only mildly elevated compared to MCL.
* ABL blasts express basophil-specific markers (e.g., BB1, 2D7) which are absent in MCL.

Chronic Basophilic Leukemia (CBL)

* Features mature or hypogranulated basophils expressing tryptase but not CD117.
* Peripheral blood basophilia is prominent, unlike in MCL.

Tryptase-Positive Acute Myeloid Leukemia (T+ AML)

* AML subtype with elevated serum tryptase and some tryptase expression on blasts.
* Unlike MCL, blasts are CD34-positive and CD117-negative or weak, and CD25 is absent.

Other Acute Leukemias

* All other acute leukemias (AML, ALL) should be excluded via immunophenotyping and genetic testing.

**EPIDEMIOLOGY**

Epidemiology of Mast Cell Leukemia (MCL):

* MCL is an extremely rare and aggressive subtype of systemic mastocytosis (SM), representing about 1% of all SM cases and approximately 4% of advanced SM cases.
* The prevalence of MCL is estimated at less than 1 per 1,000,000 people globally, making it one of the rarest hematologic malignancies.
* Studies report a median age at diagnosis ranging from 52 to 63 years, with cases documented from adolescence (as young as 5 years) to elderly (up to 90 years).
* Gender distribution varies:
  + Some studies show a female predominance (female:male ratio ~1.5:1)
  + Other data, such as from the National Cancer Database (NCDB), indicate a slight male predominance (~53% males).
* Most patients are White and non-Hispanic, with the majority residing in metropolitan areas and treated at academic or research centers.
* MCL can present as primary (de novo) in about 70% of cases or as secondary (following other forms of mastocytosis) in around 30%.
* Clinical presentation involves multi-organ involvement including bone marrow, liver, spleen, gastrointestinal tract, and others.
* The 5-year overall survival rate is very poor, approximately 16.6%, reflecting the aggressive nature of the disease.
* Incidence trends show a gradual increase in diagnosis over time, likely due to improved awareness and diagnostic method

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**AGGRESSIVE NATURAL KILLER CELL LEUKEMIA**

**DEFINITION AND DESCRIPTION**

Aggressive natural killer (ANK) cells belong to a group of white blood cells called “lymphocytes” which play a vital role in the body’s immune system. NK cells in particular target and destroy disease-causing pathogens, and detect and control the early signs of cancer.

In ANKL, the NK cells are unable to perform their usual functions. The accumulation of cancerous or “neoplastic” NK cells in the body leads to serious and life threatening complications.

## **Symptoms of ANKL**

ANKL can present differently from person to person. However, the most common signs and symptoms include:

* fever
* night sweats
* unintentional weight loss
* swelling of the lymph nodes

People with ANKL commonly present with a rare and life threatening inflammatory condition called “fulminant hemophagocytic lymphohistiocytosis (HLH). This condition occurs as a result of immune system overactivation, and can lead to multiple organ failure. Common HLH triggers include:

* infection, with Epstein-Barr virus (EBV), which is the most common cause
* acute illness
* cancer

The two most common clinical features of HLH are fever and enlargement of the spleen (splenomegaly). The latter may cause symptoms such as:

* abdominal discomfort
* pain in the upper left abdomen
* referred pain in the upper left shoulder
* abdominal bloating
* feeling full after eating very little (early satiety)
* weight loss

## **Causes and risk factors of ANKL**

Due to the rarity of NKL, scientists are still working to determine its causes and risk factors.

While anyone can develop ANKL, the average age at disease onset is 40 years, and the disease is more common among people of Asian ethnicity.

EBV infection is a risk factor for ANKL. As the Centers for Disease Control and Prevention (CDC) explains, EBV is among the most common human viruses in the world, and most people develop EBV at some point in their lifetime. Children rarely experience symptoms, while teenagers and adults may experience symptoms for several weeks or months.

### **The role of Epstein-Barr virus in ANKL**

Once a person has had EBV, the virus becomes inactive or “latent” in their body. However, the virus can express viral proteins that disrupt cell functioning, suppress cell death, and trigger uncontrolled cell growth. This, in turn, can increase the risk of certain cancers.

Cases of ANKL that are associated with EBV infection are referred to as “EBV-positive”.

ANKL can also develop in people who have never had EBV. Doctors refer to this type of ANKL as “EBV-negative”. Unlike EBV-positive ANKL, EBV-negative ANKL occurs most often in older adults and arises equally among people of Asian and non-Asian ethnicity.

However, EBV-positive and EBV-negative ANKL appear equally aggressive in terms of their clinical onset and disease course.

## **Diagnosis and test**

Doctors may have difficulty accurately diagnosing ANKL due to the following:

* The disease is rare and has a rapid onset.
* The disease has no specific pathologic features and shares symptoms with many other conditions.
* The disease has no standard immunophenotypic features, meaning that the diseased cells do not show any features specific to ANKL, such as specific antigens or markers on their surface.

ANKL can be particularly difficult to diagnose in its early stages due to the small number of cancerous NK cells in the bone marrow. According to some studies, this number may be as low as 5% or even less.

As the disease progresses, the number of cancerous NK cells in the bone marrow rapidly increases. As such, the reviewers recommend that doctors conduct multiple blood or bone marrow specimens at various time points to check for the disease.

Once doctors have retrieved a blood or bone marrow sample, they will send it to a lab for analysis using flow cytometry. This analysis helps determine the types of cells, their characteristics, and the presence of tumor markers.

## **Treatment for ANKL**

Treatment for ANKL typically involves chemotherapy, radiation therapy, or a combination of the two. Large-scale clinical studies are necessary to determine the optimal treatment approach. A person with ANKL can consider talking with their doctor about the possibility of joining clinical trials.

Combined radiation therapy and chemotherapy regimens incorporating the chemotherapy drug “L-asparaginase” appear most effective for treating ANKL. An example of such a regimen is the “SMILE” regimen, which consists of the following drugs:

* dexamethasone
* methotrexate
* ifosfamide
* L-asparaginase
* etoposide

## **outlook for ANKL**

The outlook for ANKL is typically very poor, even among individuals on the more successful treatment regimens, such as SMILE.

In a small, older study from 2016, only 50% of 13 individuals on the SMILE regimen experienced a partial or complete response to treatment, with only 27.8% experiencing a complete response to treatment. Eight individuals then received a follow-up blood and bone marrow transplant called “hematopoietic stem cell transplantation (HSCT)”, which involves implanting stem cells to promote healthy blood cell production. Six individuals remained alive following the procedure.

A 2017 study of 21 people with ANKL also demonstrated improved survival rates among those who received HSCT following their initial treatment. Of the 17 individuals who received an L-asparaginase-containing regimen, 14 experienced a complete treatment response prior to HSCT.

At 25-month follow-up, the 2-year progression-free survival (PFS) was 20%, and the overall survival (OS) was 24%. The term “PFS” refers to the length of time a person lives with a disease without it worsening, while the term “OS” refers to the average length of time a person lives following their initial diagnosis.

**EPIDEMIOLOGY**

Epidemiology of Aggressive NK-Cell Leukemia (ANKL):

* ANKL is a very rare and highly aggressive hematologic malignancy derived from natural killer (NK) cells.
* It predominantly affects young to middle-aged adults, with a median age at diagnosis typically between 30 and 40 years.
* There is a marked geographic and ethnic predilection, with the highest incidence reported in East Asia (especially Korea, Japan, and China) and parts of Central and South America.
* ANKL is extremely rare in Western countries, with only sporadic cases reported.
* The disease shows a slight male predominance.
* Due to its rarity, precise incidence and prevalence data are limited, but it is estimated to account for less than 1% of all leukemias.
* ANKL is strongly associated with Epstein-Barr virus (EBV) infection, which is detected in the leukemic NK cells in most cases, especially in endemic areas.
* The disease has a rapid clinical course, often presenting with systemic symptoms, hepatosplenomegaly, and bone marrow failure.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Aggressive NK-Cell Leukemia (ANKL) includes several hematologic malignancies and related disorders with overlapping clinical, morphologic, immunophenotypic, and genetic features. Based on the latest expert sources, the key differential diagnoses are:

Extranodal NK/T-Cell Lymphoma, Nasal Type (ENKTL)

* Shares many immunophenotypic and morphological features with ANKL, including strong association with Epstein-Barr virus (EBV) infection and expression of NK-cell markers (CD2, CD56, cytoplasmic CD3ε).
* ENKTL typically involves the upper aerodigestive tract (nasal cavity, nasopharynx) but can disseminate to other organs including bone marrow.
* Clinical presentation is generally less aggressive than ANKL.
* Genetic differences: ANKL often shows gains of 1q and losses of 7p15.1-p22.3 and 17p13.1, which may help distinguish it from ENKTL.

## Chronic Lymphoproliferative Disorder of NK Cells (CLPD-NK)

* Indolent NK-cell proliferation without EBV association.
* Characterized by uniform CD8 positivity and loss of CD2 expression, unlike ANKL.
* Clinical course is much less aggressive; many patients are asymptomatic or have mild cytopenias.

## EBV-Associated Hemophagocytic Lymphohistiocytosis (EBV-HLH)

* A severe hyperinflammatory syndrome triggered by EBV infection, often with expansion of T or NK cells.
* Can mimic ANKL clinically with fever, hepatosplenomegaly, cytopenias, and coagulopathy.
* Distinguishing features include lack of clonal NK-cell proliferation and absence of neoplastic NK cells on flow cytometry or biopsy.

## Systemic EBV-Positive T-Cell Lymphoma of Childhood

* Aggressive EBV-driven T-cell lymphoma presenting with systemic symptoms and HLH, mainly in children.
* Immunophenotype shows T-cell markers rather than NK-cell markers.

## Primary Effusion Lymphoma (PEL)

* A rare lymphoma presenting as effusions without tumor masses, sometimes involving NK cells.
* Distinguished by presence of HHV-8 infection and lack of EBV association in many cases.

## Other NK-Cell Neoplasms

* Blastic NK-cell lymphoma/leukemia (rare) and other mature NK-cell neoplasms need to be considered.

Reference

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### **Lymphoma**

**Definition and description**

Lymphoma affects the lymphatic system, where abnormal lymphocytes multiply in lymph nodes, weakening immunity. It accounts for about half of blood cancer cases annually

Lymphoma is a cancer of the lymphatic system. The lymphatic system is part of the body's germ-fighting and disease-fighting immune system. Lymphoma begins when healthy cells in the lymphatic system change and grow out of control.

The lymphatic system includes lymph nodes. They are found throughout the body. Most lymph nodes are in the abdomen, groin, pelvis, chest, underarms and neck.

The lymphatic system also includes the spleen, thymus, tonsils and bone marrow. Lymphoma can affect all these areas and other organs in the body.

Lymphoma” is the general term for cancer in your lymphatic system — the network of tissues, vessels and organs that help your body fight infection. It’s considered a blood cancer because the condition starts in white blood cells (lymphocytes) in your lymphatic system.

There are many types of lymphoma. The main subtypes are:

* Hodgkin lymphoma (formerly called Hodgkin disease).
* Non-Hodgkin lymphoma.

Many treatments for lymphoma exist. The treatment that's best for you will depend on the type of lymphoma you have. Treatments can control the disease and give many people with lymphoma the chance of a full recovery.

## Stages

* Stage 1 : In this stage, the lymphoma only affects a single group of lymph nodes (glands). It can occur anywhere in the body, above or beneath the diaphragm, and not just in the neck.
* Stage 2 : It is the advanced stage of lymphoma. The term "advanced lymphoma" refers to lymphoma originating in the lymph nodes and progressing to at least one organ outside the lymphatic system, such as the bone marrow, lung, and liver.
* Stage 3 : At least two groups of lymph nodes have lymphoma. These may be located everywhere on the body. However, they are located on the same side of the stomach to be classified as stage 2 lymphoma.
* Stage 4 : In this stage, the lymph nodes affected by lymphoma are located on both sides of the stomach.
* Stage 5 : The lymphoma spreads to one or more groups of lymph nodes and originates in a single organ (except the lymphatic system). It must be on the single side of the stomach.

### **Signs and symptoms**

### of lymphoma may include:

Many lymphoma symptoms are like symptoms of other, less serious diseases. Having these symptoms doesn’t mean that you have lymphoma. But you should consider talking to a healthcare provider whenever you have changes in your body that don’t go away within a few weeks.

Symptoms common to Hodgkin lymphoma and non-Hodgkin lymphoma can include:

* Painless swelling of one or more lymph nodes in your neck, armpits or groin that doesn’t go away within a few weeks.
* Persistent fatigue, when you feel very tired day after day even after getting enough sleep.
* Fever stays above 103 degrees Fahrenheit (39.5 degrees Celsius) for more than two days, or a fever that comes back.
* Drenching night sweats, sweating that are so intense that you wake up to find your pajamas and sheets soaking wet.
* Shortness of breath (dyspnea), when you feel as if you can’t get enough air in your lungs.
* Unexplained weight loss, when you’ve lost 10% of your total body weight over six months without dieting or exercise.

### **Causes of lymphoma**

Lymphoma happens when the white blood cells in your lymphatic system change (mutate) into rapidly growing cancer cells that don’t die. Like most cancers, the majority of the genetic mutations that cause lymphoma happen spontaneously, without an identifiable cause. But research suggests the following conditions or issues may increase your risk of developing lymphoma:

* You have or have had viruses including HIV (human immunodeficiency virus), Epstein-Barr (mononucleosis) and Kaposi sarcoma human immunodeficiency virus.
* You have a family history of lymphoma.
* Your immune system is weakened by other conditions or medical treatments. For example, people who have organ transplants take immunosuppressant medication to keep their bodies from rejecting the transplanted organ.
* You have an autoimmune disease. An autoimmune disease happens when your immune system accidentally attacks your body instead of protecting it.

Healthcare professionals aren't sure what causes lymphoma. Lymphoma begins with changes in the DNA of a disease-fighting blood cell called a lymphocyte.

A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA gives instructions to grow and multiply at a set rate. Healthy cells die at a set time.

In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to make more cells quickly. The cancer cells can go on living when healthy cells die.

In lymphoma, the DNA changes happen in the lymphocytes. The changes can:

* Lead diseased lymphocytes grow out of control.
* Cause too many diseased lymphocytes in the lymph nodes.
* Cause the lymph nodes, spleen and liver to swell.

## **Risk factors**

Some factors can increase the risk of lymphoma. They include:

* **A weakened immune system.** If the immune system is weakened by medicines or illness, there might be a higher risk of lymphoma. People with a weakened immune system include those taking medicines to control the immune system, such as after an organ transplant. Certain health conditions, such as infection with HIV, also can weaken the immune system.
* **Family history.** People who have a parent, sibling or child with lymphoma are at higher risk of the disease.
* **Specific infections.** Some infections increase the risk of developing lymphoma. Examples include Epstein-Barr virus, Helicobacter pylori and HIV.
* **Your age.** Some types of lymphoma are more common in teens and young adults. Others happen more often in people over 55.

**Treatment**

The treatment for lymphoma depends on age, type of lymphoma, stage of lymphoma, and overall health of the patient. The different methods used for the treatment of lymphoma are:

* **Surgery**:The surgery aims to remove the affected spleen and lymph nodes as much as possible. It is usually performed in early-stage lymphoma.
* Bone marrow transplant:In this, a high dose of chemotherapy or radiation are given to kill the lymphoma and suppress the bone marrow. The destroyed bone marrow is later replaced with healthy stem cells.
* Radiation therapy:Radiation therapy is usually more effective on lymphoma cells than any other type of cancer cells, as lymphoma cells are sensitive to radiation. It is used to treat early-stage lymphoma that is confined to one part of the body. In this, high-powered beams are used to kill the cancerous cells. Radiation therapy may be combined with surgery or chemotherapy when the tumor is very bulky and is not removed (by surgery) or killed (by chemotherapy).
* **Chemotherapy**:Chemotherapy involves using drugs that kill the lymphoma cells by interfering in cell division. Chemotherapy is also used in relieving the symptoms in patients with advanced lymphoma as a part of palliative care.
* Immunotherapy:Immunotherapy enables the immune system to recognize unique proteins on the surface of lymphoma and attack them. These drugs also strengthen the immune system.
* **Targeted therapy**:Targeted therapy targets the abnormalities or weaknesses of the lymphoma cells and targets them. It attacks the lymphoma cells more precisely than chemotherapy and causes less damage to the healthy cells.

## Prevention

The risk of lymphoma can be reduced by:

* Maintaining a healthy BMR
* Avoiding activities that increase the chance of getting infected with AIDS and hepatitis C
* Avoiding unnecessary exposure to harmful chemicals and radiation, as overexposure to industrial and agricultural chemicals enhances the risk of lymphoma
* Getting regularly screened after the age of 50
* Quitting smoking
* Following a healthy eating pattern
* Being physically active

### **Prognosis of Lymphoma**

### The five-year survival rate describes the percentage of people who live at least five years after being diagnosed with a particular type of cancer.According to the American Cancer Society, the overall five-year survival rate for NHL is 74 percent. It’s important to note that these figures are variable for each subtype of NHL. The five-year relative survival rate for people with localized Hodgkin lymphoma is about 93 percent. It’s about 83 percent for those with distant-stage disease (when the cancer has spread to areas such as the lungs, liver, or bone marrow). The survival rates have steadily improved for this type of cancer in recent years. Hodgkin lymphoma is now considered one of the most curable forms of cancer. It’s important to remember that survival rates are only estimates. Your outlook will depend on several factors, including the type of lymphoma you have and how aggressive your disease is, as well as your age and general health.

## **Duration of Lymphoma**

While treatment for lymphoma is often successful and leads to complete remission, for some patients, lymphoma may be a chronic illness. The cancer doesn’t go away, but with ongoing treatment and close monitoring, it can be controlled and might not grow or spread for months or years.

**Treatment and Medication Options for Lymphoma**

Treatment options are different for Non-Hodgkin Lymphomas and Hodgkin Lymphomas. And treatment will also depend on the stage of the cancer, among other factors.

## **Complications of Lymphoma**

Treatments for Hodgkin and non-Hodgkin lymphoma are now so varied and effective that many patients will be cured and live long lives after diagnosis and treatment. But there can be complications as a result of treatment. Depending upon the type of treatment and the health of the patient, doctors will watch for heart disease, secondary cancers (elsewhere in the body), lung and bone health, and cognitive and memory problems. Regular follow-up care is essential.

**Epidemiology**

In 2020, over 101,133 cases and over 32,560 deaths occurring from HL were reported globally by GLOBOCAN in 2018, and this malignancy can be cured in most cases . The outstanding characteristic expression of this malignancy occurs in approximately ≤1% of neoplasm . It is estimated that approximately ≤ 1 of 25,000 people are affected by this cancer annually and accounts for about 1% of all cancers that occur in the world. According to IARC, GLOBOCAN , the occurrence of Hodgkin lymphoma is 2.7-2.8 per 100,000 persons annually (2.44/100,000 persons in Nigeria), however this varies considerably by age, gender, ethnic groups, geographical regions and socio-economic status . Also recent statistics of IARC, GLOBOCAN estimates 79,990 i.e. 0.4% incidence with mortality of 26,167 i.e. 0.3% cancer incidence globally . There has been an upsurge in the incidence trend of Hodgkin lymphoma. Studies from GDB reveal data on the rise in rates of HL from 72,937 to 101,133 cases and mortality of 35,946 to 32,560 between 1990-2017 . HL is an unusual neoplasm, with 7000-7500 new diagnoses yearly in the United States and United Kingdom and majority of the affected people are diagnosed at the early occurrence of the disease .

In Nigeria, about 2030 cases were diagnosed in 2020 and a 5-year prevalence of 5031. Also in the Mediterranean basin populations such as France and Italy, incidence rates are estimated at 2.51 male to 2.74 female and 2.76 male to 2.02 female, respectively with mortality occurrence at 0.29 and 0.37 respectively , whereas incidence and mortality in Nigeria is estimated at 1.6% and 1.2%, the mortality is about 4 times the risk of death in other regions . HL can affect individuals of any age, however, occurs frequently between two age groups specifically i.e. 15-35 and above 55 years respectively. Generally occurrence of lymphomas in Africa is very minimal including association of risk factors such as HIV. HL incidence in Nigeria is similar to the incidence in other regions but there is a higher death rate in Nigeria, hence this review focuses on HL in Nigeria to review the clinical patterns, trends and contributory factors to the incidence of HL and how this can be overcome. HL ranked the 12th most common cancer in Nigeria with 2030 new cases and 919 deaths reported in 2020 . We reviewed briefly other reported studies on incidence, clinicopathological features and frequency of occurrence of Hodgkin lymphoma. A 25 year review of cases seen at the University of Benin teaching hospital presents a dual-peak occurrence of HL between 11-15 and 21-25 years respectively as well as a statistically significant difference between age and gender distribution. Olu-Eddo reported 56 (6.8%) cases of HL, most of which were mixed cellularity HL subtype (64.3%) and lymphocyte depleted HL (19.6%). A fifteen-year epidemiological study of histopathological examination of lymphomas conducted in Ibadan showed that the lymphoma was identified in 51 males and 29 females between ages of 5 - 74 years and about 60% occurred in ages below 40 while modal group occurrence was in their thirties. Sites of occurrence were frequent at a nodule and others occurring at several nodal sites, such as intestine, liver, and spleen . A case study in the north east region of Nigeria evaluating lymphomas in 50 cases studied the patterns of presentations relative to sex, stating that 10 cases were of Hodgkin lymphoma with ratio 4:1 male and female respectively. Patterns of presentations revealed the following; 4 cases in stage II, 3, 2 and 1 were diagnosed to be I, III, and IV stages of HL respectively . In Ile-Ife, of eighty-three histological samples of lymphoma cases, about 20.5% were identified as cHL, presenting frequently the cellular mixture subtype and eleven cases were observed to be associated with Epstein Barr virus . Kolawole in a recent study on histological assessment of samples retrieved from different laboratories in Lagos, conducted in LUTH, indicated a sudden rise in incidence of HL. Thirty cases were identified as HL, two were marked as NLPHL, HL subtypes; NSHL, MCHL AND LRHL were estimated at 40%, 23.3%, and 10%, respectively above 7 years. This malignant disease displays a bimodal curve of its occurrence in more advanced nations. Also, the occurrence rate is said to be stable for over twenty years . In the less advanced nations, the entire occurrence of Hodgkin lymphoma is lesser when compared to advanced nations excluding children below 15 years, where a higher occurrence is observed. Just a slight raised level of occurrence is observed throughout adolescence and young adulthood . Generally the malignant neoplasm has been identified to persist more in males compared to females. In 2010, Worldwide it resulted in approximately 18,000 deaths downward from 19,000 deaths in 1990 . Another recent re-classified lymphomas cases from formalin fixed paraffin embedded tissues using WHO classification, and reports higher male to female ratio, ethnic variations in the lymphoma cases; CLL was prevalent in the Hausa compared to HL in the Yoruba ethnic while the Igbo ethnic group reported similar distribution of CLL, HL, and diffuse large B-cell lymphomas not otherwise specified (DLBCL, NOS).

## **Diagnostic Considerations**

Other conditions to consider in the differential diagnosis of Hodgkin lymphoma include the following:

* Any disease presenting with lymphadenopathy and constitutional symptoms
* Infection with human immunodeficiency virus (HIV)
* Hypersensitivity reaction
* Other solid tumors
* Non-Hodgkin lymphoma, particularly diffuse large B cell lymphoma and anaplastic large cell lymphoma, both of which may have CD30 expression

Because Hodgkin lymphoma is considered a curable malignancy and the differential diagnosis is broad, medicolegal problems may arise from failure to diagnose the disease in a timely manner, possibly due to the following factors:

* The misinterpretation of B symptoms
* A lack of follow-up for abnormal chest radiographs or physical examination findings
* A missed pathologic diagnosis because a needle biopsy was obtained rather than an excisional lymph node biopsy

Occasionally, Hodgkin lymphoma can present as hemophagocytic syndrome (hemophagocytic lymphohistiocytosis).The hemophagocytic syndrome may be more prevalent in patients with Epstein-Barr virus (EBV) antigen expression and has the following characteristics:

* Pancytopenia
* Fever
* Hepatosplenomegaly with liver function test abnormalities
* Elevated serum levels of ferritin and triglycerides
* Phagocytosis of hematopoietic lineage cells by benign macrophages

## **Differential Diagnoses**

* Cytomegalovirus (CMV)
* Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
* Non-Hodgkin Lymphoma (NHL)
* Physical Medicine and Rehabilitation for Systemic Lupus Erythematosus
* Sarcoidosis

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**HODGKIN LYMPHOMA**

**DEFINITION AND DESCRIPTION**

Hodgkin lymphoma is a type of cancer that affects the lymphatic system. The lymphatic system is part of the body's germ-fighting and disease-fighting immune system. Hodgkin lymphoma begins when healthy cells in the lymphatic system change and grow out of control.

The lymphatic system includes lymph nodes. They are found throughout the body. Most lymph nodes are in the abdomen, groin, pelvis, chest, underarms and neck.

The lymphatic system also includes the spleen, thymus, tonsils and bone marrow. Hodgkin lymphoma can affect all these areas and other organs in the body.

Hodgkin lymphoma, which used to be called Hodgkin disease, is one of two broad types of lymphoma. The other is non-Hodgkin lymphoma.

Advances in diagnosis and treatment of Hodgkin lymphoma have helped give people with this disease the chance for a full recovery.

**Causes**

Healthcare professionals aren't sure what causes Hodgkin lymphoma. It begins with changes in the DNA of a disease-fighting blood cell called a lymphocyte. A cell's DNA contains the instructions that tell the cell what to do.

The DNA changes tell the cells to multiply quickly and live when other cells would naturally die. The Hodgkin lymphoma cells attract many healthy immune system cells to protect them and help them grow. The extra cells crowd into the lymph nodes and cause swelling and other symptoms.

There are multiple types of Hodgkin lymphoma. The type of lymphoma you have is based on the characteristics of the cells involved in your disease and their behavior. The type of lymphoma you have helps determine your treatment options.

### **Classical Hodgkin lymphoma**

Classical Hodgkin lymphoma is the more common type of this disease. People diagnosed with this type have large lymphoma cells called Reed-Sternberg cells in their lymph nodes.

Subtypes of classical Hodgkin lymphoma include:

* Nodular sclerosis Hodgkin lymphoma.
* Mixed cellularity Hodgkin lymphoma.
* Lymphocyte-depleted Hodgkin lymphoma.
* Lymphocyte-rich Hodgkin lymphoma.

### **Nodular lymphocyte-predominant Hodgkin lymphoma**

This type of Hodgkin lymphoma is much rarer. It involves lymphoma cells sometimes called popcorn cells because of how they look. Usually, it is diagnosed early and may need less intensive treatments than the classical type of Hodgkin lymphoma.

**Risk factors**

Factors that can increase the risk of Hodgkin lymphoma include:

* **Your age.** Hodgkin lymphoma is most often diagnosed in people in their 20s and 30s and those over age 65.
* **A family history of Hodgkin lymphoma.** Having a blood relative with Hodgkin lymphoma increases the risk of Hodgkin lymphoma.
* **Being male.** People who are assigned male at birth are slightly more likely to develop Hodgkin lymphoma than are those who are assigned female at birth.
* **Past Epstein-Barr infection.** People who have had illnesses caused by the Epstein-Barr virus are at higher risk of Hodgkin lymphoma than are those who haven't. One example is infectious mononucleosis.
* **HIV infection.** People who are infected with HIV have an increased risk of Hodgkin lymphoma.

There's no way to prevent Hodgkin lymphoma.

**SYMPTOMS**

Signs and symptoms of Hodgkin lymphoma may include:

* Painless swelling of lymph nodes in the neck, armpits or groin.
* Fever.
* Feeling very tired.
* Night sweats.
* Weight loss that happens without trying.
* Itchy skin.

## **Diagnosis and test**

Hodgkin lymphoma diagnosis often begins with an exam that checks for swollen lymph nodes in the neck, underarm and groin. Other tests include imaging tests and removing some cells for testing. The type of tests used for diagnosis may depend on the lymphoma's location and your symptoms.

### **Physical exam**

A healthcare professional may start by asking about your symptoms. The health professional also may ask about your health history.

Next, the healthcare professional may feel and press on parts of your body to check for swelling or pain. To find swollen lymph nodes, the healthcare professional may feel your neck, underarms and groin. Be sure to say if you have felt any lumps or pain.

### **Blood tests**

A sample of your blood is examined in a lab to understand your health and look for signs of cancer.

### **Biopsy**

A biopsy is a procedure to remove a sample of tissue for testing in a lab. For Hodgkin lymphoma, the biopsy typically involves removing one or more lymph nodes. The lymph nodes go to a lab for testing to look for cancer cells. Other special tests give more details about the cancer cells. Your healthcare team uses this information to make a treatment plan. Sometimes a biopsy is taken from other parts of the body, such as the liver, to look for signs of Hodgkin lymphoma.

### **Imaging tests**

Your healthcare team may recommend imaging tests to look for signs of lymphoma in other areas of your body. Tests may include a chest X-ray, CT, MRI and positron emission tomography scans, also called PET scans.

### **Bone marrow aspiration and biopsy**

Bone marrow aspiration and biopsy are procedures that involve collecting cells from the bone marrow. The cells are sent for testing. Tests can look for Hodgkin lymphoma cells.

### **Hodgkin lymphoma stages**

Your test results are used to assign a stage to your Hodgkin lymphoma. The stage helps determine the seriousness of your condition and the treatments most likely to help you.

Hodgkin lymphoma staging uses the numbers 1 to 4 to indicate the stage. A lower number means the lymphoma cells only involve one or a few areas of lymph nodes. An early-stage cancer is more likely to be cured. As the lymphoma grows to involve more areas of the body, the stage number goes up. A higher number means the cancer is more advanced.

Hodgkin lymphoma stages also may include the letters A and B. The letter A means that you don't have worrying symptoms of lymphoma. The letter B means that you have some symptoms, such as fever or weight loss.

**Treatment**

Many types of treatments exist for Hodgkin lymphoma. Treatment often starts with chemotherapy. Your healthcare team might check to see how the lymphoma is responding and decide whether you need more treatment. Your options might include radiation therapy, chemotherapy, immunotherapy, targeted therapy and bone marrow transplant, also called stem cell transplant. Sometimes, a combination of treatments is used.

The treatment that's best for you depends on the type of Hodgkin lymphoma that you have. Your healthcare team also might consider the stage of your lymphoma, whether you have any symptoms and your overall health.

### **Chemotherapy**

Chemotherapy treats cancer with strong medicines. Many chemotherapy medicines exist. Most chemotherapy medicines are given through a vein. Some come in pill form.

Classical Hodgkin lymphoma treatment usually involves a combination of chemotherapy and radiation therapy. Sometimes chemotherapy may be the only treatment needed. More-advanced disease may be treated with a combination of chemotherapy and medicines that attack specific chemicals in cancer cells, known as targeted therapy.

For nodular lymphocyte-predominant Hodgkin lymphoma, chemotherapy may be combined with targeted therapy and radiation therapy.

Side effects of chemotherapy depend on the medicines you're given. Common side effects are nausea and hair loss. Serious long-term complications can occur, such as heart disease, lung damage, fertility problems and other cancers.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. During radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body.

For Hodgkin lymphoma, radiation can be aimed at affected lymph nodes and the nearby areas where the disease might spread. It's usually used with chemotherapy. Radiation therapy may be the only treatment needed for early-stage nodular lymphocyte-predominant Hodgkin lymphoma.

Radiation therapy side effects include fatigue and a sunburn-like reaction on the skin at the site where the radiation is aimed. Other side effects depend on where the radiation is aimed. Radiation to the neck can cause dry mouth and hurt the thyroid. Radiation to the chest can hurt the heart and lungs.

### **Bone marrow transplant**

A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments. A bone marrow transplant may be an option if Hodgkin lymphoma returns or doesn't respond to other treatments.

During a bone marrow transplant, your own blood stem cells are removed, frozen and stored. Next, you receive high-dose chemotherapy and radiation therapy to destroy cancer cells in your body. Finally, the stored stem cells are thawed and put back in your body to help build healthy bone marrow.

There is an increased risk of infection after a transplant.

### **Targeted therapy**

Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in cancer cells. By blocking these chemicals, targeted therapy can cause cancer cells to die. Targeted therapy is often combined with chemotherapy for treating nodular lymphocyte-predominant Hodgkin lymphoma.

For classical Hodgkin lymphoma, targeted therapy might be an option in certain situations.

### **Immunotherapy**

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

For Hodgkin lymphoma, immunotherapy might be considered in certain situations, such as if the disease doesn't respond to other treatments.

**Alternative medicine**

No alternative medicines have been found to treat Hodgkin lymphoma. But integrative medicine may help you cope with the stress of a cancer diagnosis and the side effects of cancer treatment.

Talk with your healthcare professional about your options, such as:

* Art therapy.
* Exercise.
* Meditation.
* Music therapy.
* Relaxation exercises.
* Spirituality.

### **When to see a doctor**

Make an appointment with a doctor or other healthcare professional if you have ongoing symptoms that worry you. Hodgkin lymphoma symptoms are like those of many more-common conditions, such as infections. The healthcare professional may check for those causes first.

# **Key Statistics for Hodgkin Lymphoma**

The American Cancer Society’s estimates for Hodgkin lymphoma in the United States for 2025 are:

* About 8,720 new cases (4,840 in males and 3,880 in females)
* About 1,150 deaths (720 males and 430 females)

Children and adults can develop Hodgkin lymphoma, but it's most common in early adulthood (especially in a person’s 20s). The risk of Hodgkin lymphoma rises again in late adulthood (after age 55). Overall, the average age of people when they are diagnosed is 39.

Hodgkin lymphoma is rare in children younger than 5 years old. But it's the most common cancer diagnosed in adolescents ages 15 to 19 years.

Incidence rates have declined by about 1% each year for Hodgkin lymphoma since the mid-2000s.

Treatments used today cure about 8 out of 10 cases of Hodgkin lymphoma (HL). Still, important research is going on in many university hospitals, medical centers, and other institutions around the world. Scientists are getting closer to finding out what causes the disease and how to better treat it. This is of special interest for hard-to-treat cases, like those that don't respond to current treatments or come back after treatment. Doctors are also looking for ways to limit the long-term side effects linked to HL treatment.

## **Imaging tests**

PET/CT scans are commonly used to help doctors stage HL and decide how much treatment needs to be given. Doctors are also looking at whether PET/CT scans done during treatment can help decide if more or less treatment is needed.

Researchers are trying to find out if MRI scans might work as well in children and teens with HL. If so, it would mean less radiation exposure and the resulting long-term side effects in young people.

## **Treatment**

Overall cure rates for HL are high, but long-term side effects of treatment are an important issue. A very active area of research is directed at learning which patients can be treated with gentler therapy and which patients need stronger treatment.

### **Radiation**

Doctors are looking to see which patients (especially children) might do just as well with lower doses of radiation, or even no radiation . They're also studying if newer forms of radiation therapy, such as intensity-modulated radiation therapy (IMRT) and proton therapy, might be useful for HL. These approaches focus radiation more precisely on tumors, which limits the doses reaching nearby normal tissues.

### **Chemotherapy**

A related area of research is finding less-toxic treatments that have fewer serious long-term side effects, yet still cure as many patients as possible. Lower doses of chemotherapy (chemo), as well as new chemo drugs and drug combinations are being studied. Many of these drugs are already used to treat other cancers and have shown promise against HL that has come back (relapsed) after other chemo treatments. Studies are in progress to see if these drugs could work better than the ones now in use.

Doctors are also looking for better chemo drugs to use with stem cell transplant. Again, improving outcomes while limiting long-term side effects is the goal.

Another approach is using newer drugs that better target HL cells. Some of these are described below.

### **Targeted therapy**

Newer drugs that work differently from standard chemo drugs are now being studied. Researchers are learning a lot about the gene changes found in HL cells. This could lead to drugs that target these changes and spare normal cells. These are known as targeted therapy drugs. Many other types of cancer are already treated with targeted therapies.

Some of these targeted drugs are being studied in combinations, in the hope that they might work better when given together. Many are given along with other cancer treatments, like chemo and/or radiation.

### **Immunotherapy (including monoclonal antibodies)**

Immunotherapy is treatment that helps the body’s immune system find and attack cancer cells. Immunotherapy is helpful against several types of cancer, including Hodgkin lymphoma.

#### **Immune checkpoint inhibitors**

Immune system cells normally have substances on them that act as checkpoints to keep them from attacking healthy cells in the body. Cancer cells sometimes use these checkpoints to avoid being attacked by the immune system. Today, drugs that block these checkpoints are used to treat HL after other treatments have been tried. Researchers are now studying other ways to use these drugs. For instance, they're looking at whether these drugs might be used as "maintenance therapy" to keep HL from coming back after transplant. They're also testing them as a first treatment for HL. The use of immune checkpoint inhibitors in children and teens, as well as in older people who are too sick to get standard treatment, is also being studied. Several other checkpoint inhibitor drugs are being studied, too.

#### **Chimeric antigen receptor (CAR) T-cell therapy**

In this treatment, immune cells called T cells are removed from the patient’s blood and altered in the lab so they have receptors called chimeric antigen receptors, or CARs on their surface. These receptors can attach to proteins on the surface of lymphoma cells. The altered T cells are then multiplied in the lab and put back into the patient’s blood. They can then find the lymphoma cells and launch a precise immune attack against them.

This technique has shown encouraging results in early clinical trials against some hard-to-treat Hodgkin lymphomas. Doctors are still improving how they make the T cells and are learning the best ways to use them. CAR T-cell therapy is only available in clinical trials at this time.

#### **Monoclonal antibodies**

Monoclonal antibodies (mAbs) are man-made versions of immune system proteins. Some can kill cancer cells by themselves. Others have radioactive molecules or cell poisons attached to them, which help kill cancer cells. An advantage of these drugs is that they seem to target lymphoma cells while having fewer side effects than standard chemo drugs. They may be used alone or along with chemo.

Some mAbs, such as brentuximab vedotin (Adcetris) and rituximab (Rituxan), are already being used to treat some cases of HL. Researchers are now studying if these drugs might be useful in other ways. For instance, brentuximab is now being studied to see if it might be helpful earlier in the course of the disease or as part of the treatment used to get ready for a transplant. And studies are now being done to see if rituximab can help treat classic forms of HL as well as the nodular lymphocyte-predominant type. Researchers are also looking for the best way to use mAbs along with standard treatment. Many newer mAbs are now being studied, too.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Hodgkin disease (Hodgkin lymphoma, HL) involves distinguishing it from a variety of infectious, inflammatory, and neoplastic conditions that can mimic its clinical, histological, and laboratory features.

Infectious and Inflammatory Conditions

* Infectious Mononucleosis (Epstein-Barr Virus infection)
  + Presents with fever, lymphadenopathy, fatigue, and sometimes splenomegaly.
  + Lymph node biopsy shows reactive hyperplasia without Reed-Sternberg cells.
* Tuberculosis (TB)
  + Can cause chronic lymphadenopathy, fever, night sweats, weight loss.
  + Granulomas with caseous necrosis on biopsy differentiate from HL.
* Sarcoidosis
  + Noncaseating granulomas in lymph nodes.
  + May have systemic symptoms and lymphadenopathy mimicking HL.
* Brucellosis, Typhoid fever, Malaria
  + Infectious diseases with systemic symptoms and lymphadenopathy.
  + Diagnosis confirmed by serology, blood cultures, and clinical context.
* Autoimmune diseases:
  + Systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA)
  + May cause lymphadenopathy and systemic symptoms but lack neoplastic cells.
* Drug hypersensitivity reactions (e.g., DRESS syndrome)
  + Can cause lymphadenopathy, rash, eosinophilia.

Other Neoplastic and Lymphoproliferative Disorders

* Non-Hodgkin Lymphomas (NHL)
  + Includes diffuse large B-cell lymphoma, follicular lymphoma, angioimmunoblastic T-cell lymphoma, and others.
  + Immunophenotyping and histology differentiate from HL.
* Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)
  + A distinct HL subtype with different morphology and immunophenotype.
* Mediastinal Gray Zone Lymphoma
  + Shares features of classic HL and primary mediastinal large B-cell lymphoma; requires immunohistochemical and molecular studies.
* Multicentric Castleman Disease
  + Lymphadenopathy with systemic symptoms; lymph node biopsy shows characteristic features.
* Other malignancies:
  + Metastatic carcinoma, melanoma, sarcoma involving lymph nodes.

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**Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL**

**DEFINITION AND DESCRIPTION**

NLPHL is a rare type of blood cancer. It occurs when lymphocytes, a type of white blood cell in the immune system, behave abnormally. Specifically, NLPHL occurs in B lymphocytes.

There are different types of lymphoma: Hodgkin or non-Hodgkin lymphoma. NLPHL is the Hodgkin type, which means Reed-Sternberg cells are present. These are large cancerous cells found in lymph fluid. The word nodular in NLPHL means the lymphoma grows in the lymph nodes. NLPHL differs from other types of Hodgkin lymphoma due to its unique pathology, which can be examined by doctors under a microscope.

This cancer type is slow-growing and not common. NLPHL accounts for about 5 percent of all Hodgkin lymphoma cases

## **causes of NLPHL**

NLPHL develops when genetic mutations affect genes within the B lymphocytes.

Researchers are unsure about the exact causes of Hodgkin lymphoma and NLPHL. Some evidence suggests that the Epstein-Barr virus, formally known as human gammaherpesvirus 4, can cause DNA changes to B lymphocytes, which in turn can produce Reed-Sternberg cells.

DNA changes to the genes may play a role in NLPHL, but more research is needed.

## **NLPHL risk factors**

Hodgkin lymphoma risk factors include age (adults in their 20s or older than 55) and gender (male) In the case of NLPHL specifically 86 percent of 1,937 patients were younger than age 65 and 67 percent were male.

## **NLPHL symptoms**

Symptoms of nodular lymphocyte-predominant Hodgkin lymphoma may include those listed below.

* Lump in the neck, groin or armpit that doesn’t go away (usually painless)
* Unexplained fatigue
* Excessive nighttime sweating
* Weight loss
* Ongoing high fevers

Fever, night sweats and weight loss are classified as “B symptoms” in Hodgkin lymphoma patients, as these symptoms can also be caused by other health issues. Always check with the care team about any concerns regarding unexpected changes in the body.

#### Hodgkin lymphoma treatment: The care you need is one call away

Your multidisciplinary team will work with you to develop a personalized plan to treat your Hodgkin lymphoma in a way that fits your individual needs and goals.

## **NLPHL diagnosis and detection**

NLPHL is diagnosed by biopsy, a surgical procedure where all or part of a lymph node is removed and examined under a microscope to look for evidence of cancer cells. The type of biopsy used varies, based on the location of the lymph node, but either local or generalized anesthetic will be used to minimize discomfort.

If cancer is found, the care team may order additional tests to determine the stage, grade and type. These may include:

* Positron emission tomography (PET) scan
* Computed tomography (CT) scan
* Magnetic resonance imaging (MRI) test
* Blood tests

### **NLPHL stages**

**Early:** Known as stage 1 or 2, this cancer type is generally localized or found in several nearby areas of the body.

**Advanced:** Stage 3 or 4 NLPHL has spread to parts of the body distant from the original cancer.

### **NLPHL grades**

Lymphomas can be either indolent or aggressive. NLPHL is an indolent lymphoma type, meaning it typically grows slowly.

## **NLPHL treatment**

The patient's care team will discuss appropriate treatment options with the patient, taking into account the following factors:

* Cancer stage and type
* Personal preferences
* Age and overall health
* Whether or not the patient wants to have children in the future
* Symptoms

For early-stage patients without B symptoms, site radiation therapy is the most common treatment—and it may be the only treatment needed. It’s also called external beam therapy and uses external radiation beams to specifically target the tumor.

If the NLPHL is advanced, chemotherapy is the most common treatment. In some patients, chemotherapy is given and then followed with radiation.

Chemotherapy is a treatment that uses medication to kill cancer cells. A number of different chemotherapy drugs can be used for NLPHL, and sometimes several are combined together.

## Nodular lymphocyte predominant Hodgkin lymphoma survival rate

Because NLPHL is a rare type of lymphoma, survival statistics are based on small case studies. One study of 73 people with nodular lymphocyte predominant Hodgkin lymphoma found that overall 10-year survival was 94 percent, and 10-year progression-free survival was nearly 76 percent.

Keep in mind that the survival rate for NLPHL depends on a variety of factors, including the patient’s age, overall health and the extent of the disease, so the patient should always talk to his or her care team about his or her individual prognosis.

**Epidemiology of Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL):**

* NLPHL is a rare subtype of Hodgkin lymphoma, accounting for approximately 5–10% of all Hodgkin lymphoma cases.
* The annual incidence is estimated at about 0.1 to 0.3 per 100,000 persons (or roughly 1 to 3 cases per million per year) in various populations.
* NLPHL shows a marked male predominance, with a male-to-female ratio of approximately 3:1.
* The median age at diagnosis is typically in the 30 to 40 years range, with disease onset often occurring before age 40 but spanning all ages.
* Compared to classical Hodgkin lymphoma (cHL), NLPHL patients more commonly present with early-stage disease (stage I or II in over 60–80% of cases) and have a more indolent clinical course
* NLPHL predominantly involves peripheral lymph nodes (cervical, axillary, inguinal), with mediastinal involvement being rare.
* B symptoms (fever, night sweats, weight loss) are less frequent in NLPHL compared to cHL
* The prognosis is generally excellent, with 10-year overall survival rates exceeding 90% in early-stage disease.
* Despite the indolent course, NLPHL carries a risk of histologic transformation to aggressive large B-cell lymphoma in a subset of patients (around 6–9% over 10 years

**The differential diagnosis of Nodular Lymphocyte-Predominant Hodgki**n Lymphoma (NLPHL) includes several lymphoid and reactive conditions that can mimic its clinical, histologic, and immunophenotypic features. Accurate differentiation is essential due to differences in prognosis and treatment. Key differential diagnoses are:

Classical Hodgkin Lymphoma (cHL), especially Lymphocyte-Rich Subtype (LRCHL)

* LRCHL can resemble NLPHL but differs by:
  + Presence of Reed-Sternberg (HRS) cells rather than lymphocyte-predominant (LP) “popcorn” cells.
  + Neoplastic cells in LRCHL are typically CD30-positive, CD15-positive, CD20-negative, while NLPHL LP cells are CD20-positive, CD30-negative, CD15-negative.
  + LRCHL often shows mediastinal involvement; NLPHL usually involves peripheral nodes.
  + Differences in follicular dendritic cell (FDC) meshworks and T-cell rosettes.

## T-cell/Histiocyte-Rich Large B-Cell Lymphoma (THRLBCL)

* Shares some morphological overlap with NLPHL, especially NLPHL Fan pattern E (diffuse areas).
* THRLBCL is typically diffuse, not nodular, lacks LP cells, and has fewer small B cells.
* Background T cells in THRLBCL are predominantly cytotoxic phenotype, while NLPHL has more follicular helper T cells and T-cell rosettes around LP cells.
* Immunophenotyping and presence/absence of nodularity help distinguish.

## Follicular Lymphoma (Floral Variant)

* Can mimic NLPHL with nodular architecture and small B-cell background.
* Lacks LP cells and T-cell rosettes seen in NLPHL.
* Usually shows complete effacement of nodal architecture and a background of atypical, nonreactive small B cells.

## Progressive Transformation of Germinal Centers (PTGC)

* A benign/reactive condition characterized by enlarged follicles with expanded mantle zones invading germinal centers.
* Does not have LP cells or T-cell rosettes and lacks lymph node effacement.
* PTGC can coexist with NLPHL in the same lymph node.

## Other Reactive Lymphadenopathies

* Follicular hyperplasia, viral infections (e.g., infectious mononucleosis), and other benign conditions may cause lymph node changes but lack neoplastic LP cells.

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**Non-Hodgkin lymphoma**

**Definition and description**

Non-Hodgkin lymphoma is a type of cancer that affects the lymphatic system. The lymphatic system is made up of organs, glands, tubelike vessels and clusters of cells called lymph nodes. It's part of the body's germ-fighting immune system.

Non-Hodgkin lymphoma happens when germ-fighting cells in the lymphatic system grow out of control. The cells can form growths, called tumors, throughout the body.

Non-Hodgkin lymphoma is a broad group of lymphomas. There are many subtypes in this group. Diffuse large B-cell lymphoma and follicular lymphoma are among the most common subtypes. The other broad group of lymphoma is Hodgkin lymphoma.

Advances in diagnosis and treatment of non-Hodgkin lymphoma have helped improve the prognosis for people with this condition.

**CAUSES**

The cause of non-Hodgkin lymphoma often isn't known. This cancer starts when germ-fighting white blood cells called lymphocytes develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do.

DNA gives healthy cells instructions to grow and multiply at a set rate. The instructions tell the cells to die at a set time. In cancer cells, the DNA changes give other instructions. The DNA changes tell the cancer cells to make more cells quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

In non-Hodgkin lymphoma, the cancer cells often build up in the lymph nodes. They also can build up in other parts of the lymphatic system.

Non-Hodgkin lymphoma can affect the:

* Lymph nodes.
* Lymph vessels.
* Adenoids.
* Tonsils.
* Spleen.
* Thymus.
* Bone marrow.
* Rarely, parts of the body that aren't part of the lymphatic system.

### **Non-Hodgkin lymphoma types**

Non-Hodgkin lymphoma most often begins in the:

* **B cells.** B cells are a type of lymphocyte that fights infection. B cells make antibodies against foreign invaders. Most non-Hodgkin lymphoma arises from B cells. Subtypes of non-Hodgkin lymphoma that involve B cells include diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and Burkitt's lymphoma.
* **T cells.** T cells are a type of lymphocyte that kills foreign invaders directly. Non-Hodgkin lymphoma happens much less often in T cells. Subtypes of non-Hodgkin lymphoma that involve T cells include peripheral T-cell lymphoma and cutaneous T-cell lymphoma.

Treatment depends on whether non-Hodgkin lymphoma arises from B cells or T cells.

**Risk factors**

Factors that may raise the risk of non-Hodgkin lymphoma include:

* **Medicines that lower the immune response.** Taking medicines that manage the immune system after an organ transplant might raise the risk of non-Hodgkin lymphoma.
* **Infection with certain viruses and bacteria.** Certain infections seem to raise the risk of non-Hodgkin lymphoma. Viruses linked to this type of cancer include HIV and Epstein-Barr virus. Bacteria linked to non-Hodgkin lymphoma include the stomach ulcer-causing bacterium Helicobacter pylori.
* **Chemicals.** Certain chemicals, such as those used to kill insects and weeds, may raise the risk of non-Hodgkin lymphoma. More research is needed to find the possible link between pesticides and non-Hodgkin lymphoma.
* **Older age.** Non-Hodgkin lymphoma can happen at any age. But it's most common in people 60 or older.

There's no way to prevent non-Hodgkin lymphoma.

**Symptoms**

Signs and symptoms of non-Hodgkin lymphoma may include:

* Swollen lymph nodes in the neck, armpits or groin.
* Belly pain or swelling.
* Chest pain, coughing or trouble breathing.
* Feeling very tired.
* Fever.
* Night sweats.
* Weight loss without trying.

## **Diagnosis and test**

Non-Hodgkin lymphoma diagnosis often begins with an exam that checks for swollen lymph nodes in the neck, underarms and groin. Tests include imaging tests and removing some cells for testing. The tests used to detect non-Hodgkin lymphoma may depend on the cancer's location and your symptoms.

### **Physical exam**

A healthcare professional checks for swollen lymph nodes in your neck, underarms and groin. The health professional also checks for a swollen spleen or liver.

### **Blood and urine tests**

Tests of your blood and urine may help rule out an infection or other disease.

### **Imaging tests**

Tests to look for lymphoma cells in other parts of the body may include CT, MRI and positron emission tomography, also called PET.

### **Lymph node biopsy**

Your healthcare professional may suggest a lymph node biopsy to look for cancer cells. A biopsy is a procedure to remove a sample of tissue for testing in a lab. A lymph node biopsy involves removing all or part of a lymph node. In the lab, tests may show whether you have non-Hodgkin lymphoma and, if so, which type.

### **Bone marrow tests**

Bone marrow aspiration and biopsy are procedures that involve collecting cells from the bone marrow. The cells are sent for testing.

In a bone marrow aspiration, a needle is used to draw a sample of the fluid. In a bone marrow biopsy, a needle is used to collect a small amount of the solid tissue. The samples most often come from the hip bone.

### **Lumbar puncture**

A lumbar puncture involves removing some of the fluid around the spinal cord. This procedure also is called a spinal tap. A healthcare professional might recommend this test if there's concern that the lymphoma affects the fluid around the spinal cord. A lumbar puncture involves putting a small needle into the spinal canal in the lower back to withdraw the fluid.

**Treatment**

Non-Hodgkin lymphoma treatment often starts with medicines or radiation therapy. Medicines used for this cancer include chemotherapy, immunotherapy and targeted therapy.

The treatments your healthcare team chooses for you depend on your lymphoma. Your healthcare team considers the types of cells involved and how quickly the cancer is growing. Your team also considers your overall health and what you prefer.

If your lymphoma seems to be growing slowly and doesn't cause symptoms, you might not need treatment right away. Instead, you may have checkups every few months. The checkups help your healthcare team watch your condition and see if your cancer is growing.

### **Chemotherapy**

Chemotherapy treats cancer with strong medicines. There are many chemotherapy medicines. Most chemotherapy medicines are given through a vein. Some come in pill form.

For many types of non-Hodgkin lymphoma, chemotherapy is the first treatment. Sometimes it's combined with targeted therapy.

### **Immunotherapy**

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

People with certain types of non-Hodgkin lymphoma may have immunotherapy if other treatments haven't helped.

### **Targeted therapy**

Targeted therapy for cancer is a treatment that uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die.

For non-Hodgkin lymphoma, targeted therapy may be used alone. But more often, it's combined with chemotherapy. This mix may be your first treatment. It can be your second treatment if your lymphoma comes back.

### **CAR-T cell therapy**

Chimeric antigen receptor T cell therapy, also called CAR-T cell therapy, trains the immune system cells to fight non-Hodgkin lymphoma. This treatment begins with removing some white blood cells, including T cells, from the blood.

The cells are sent to a lab. In the lab, the cells are treated so that they make special receptors. The receptors help the cells recognize a marker on the surface of the lymphoma cells. Then the cells go back into the body. There they find and destroy the non-Hodgkin lymphoma cells.

CAR-T cell therapy might be an option for certain types of B-cell non-Hodgkin lymphoma. It's typically used when other treatments haven't worked.

### **Bone marrow transplant**

A bone marrow transplant, also called a bone marrow stem cell transplant, involves putting healthy bone marrow stem cells into the body. These cells replace cells hurt by chemotherapy and other treatments. People with non-Hodgkin lymphoma may have a bone marrow transplant if other treatments haven't helped.

### **Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. During radiation therapy, you lie on a table while a machine moves around you. The machine directs radiation to precise points on your body.

For certain types of non-Hodgkin lymphoma, radiation therapy may be the only treatment you need. This may be true if your lymphoma is in just one or two spots and grows slowly.

People with non-Hodgkin lymphoma also may need radiation after chemotherapy to kill any lymphoma cells that might remain. Radiation also can relieve symptoms and improve quality of life.

### **When to see a doctor**

Make an appointment with your doctor if you have any persistent signs and symptoms that worry you.

**Alternative medicine**

No alternative medicines have been found to cure non-Hodgkin lymphoma. But alternative medicine may help you cope with a cancer diagnosis and the side effects of cancer treatment. Talk with your healthcare team about your choices, such as:

* Art therapy.
* Exercise.
* Meditation.
* Music therapy.
* Relaxation exercises.
* Spirituality.

**EPIDEMIOLOGY**

* 7.1 per 100,000 people. The incidence varies geographically, with higher rates generally observed in regions with higher socio-demographic index (SDI).
* Trends:  
  From 1999 to 2021, NHL incidence showed a slow upward trend globally (average annual percentage change ~0.3%), especially in low to middle SDI regions where increases of 3–4% per year have been reported. In contrast, high SDI regions have experienced stable or slightly declining incidence rates. In the United States, incidence rates have declined by about 1% per year since 2015.
* Mortality:  
  Despite rising incidence in some areas, age-standardized mortality rates (ASMR) and disability-adjusted life years (DALYs) have declined globally (AAPC about -0.6% to -0.8% per year), reflecting improvements in treatment and diagnosis. In the US, NHL death rates decreased by about 2% per year from 2013 to 2022.
* Prevalence:  
  The age-standardized prevalence rate (ASPR) of NHL has increased, consistent with improved survival and aging populations[1](https://pubmed.ncbi.nlm.nih.gov/40165194/).
* Demographics:
  + NHL can occur at any age but is more common in older adults, with more than half of cases diagnosed in people aged 65 or older.
  + It is one of the more common cancers in children, teens, and young adults but less frequent than in older populations.
  + Males have a slightly higher incidence than females.
* Regional Variations:
  + Significant increases in NHL incidence have been observed in parts of South America (e.g., Colombia, Chile), Eastern Europe, and Central Asia.
  + Moderate decreases or stable trends have been reported in North America, Western Europe, and some parts of Asia.
  + The burden of NHL is rising more sharply in low and middle SDI regions, highlighting disparities in healthcare access and risk factor prevalence

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## **Burkitt lymphoma**

**Definition and description**

Burkitt lymphoma is a rare, fast-growing cancer of B cells — a type of white blood cell. It’s a form of non-Hodgkin lymphoma that most often affects children and young adults. Other names for this condition include Burkitt’s disease, Burkitt’s lymphoma and Burkitt’s tumor.

It typically starts in lymph nodes in your abdomen or pelvis, but it can also spread to your:

* Belly
* Bone marrow
* Gastrointestinal tract
* Jaw
* Spleen
* Throat
* Tonsils

Because it grows so fast, Burkitt lymphoma can be life-threatening. But with quick treatment, many people go into long-term remission. That means symptoms go away and stay away.

### **Types of Burkitt lymphoma**

There are three types:

* Endemic: This type is most common in parts of Africa and is linked to Epstein-Barr virus (EBV).
* Sporadic: This type is common in the U.S., especially in kids. It makes up over 40% of childhood non-Hodgkin lymphoma cases.
* Immunodeficiency-related: This affects people with weakened immune systems, like those with HIV/AIDS.

## **Symptoms and Causes**

Symptoms can appear suddenly and include:

* Belly pain, nausea or vomiting
* Fever, tiredness and night sweats
* Loss of appetite and unintended weight loss
* Swollen lymph nodes

These symptoms can look like common illnesses, but if they get worse, see a healthcare provider. Burkitt tumors can double in size within days.

### **Burkitt lymphoma causes**

Experts don’t know exactly what causes Burkitt lymphoma. It’s linked to changes (variations) in a gene called *MYC*, which helps control cell growth. A type of genetic glitch, called translocation, can cause this gene to become overactive.

In the U.S., some people who have Epstein-Barr virus (EBV) also have Burkitt lymphoma. But not everyone who has EBV develops Burkitt lymphoma.

#### **Complications**

Possible complications include:

* Low blood cell counts, needing transfusion of blood products
* Tumor lysis syndrome
* Weakened immunity

Tell your provider if your symptoms become hard to manage.

## **Diagnosis and Tests**

To diagnose Burkitt lymphoma, your provider may start with a lymph node biopsy. Other tests may include:

* CT scan: Looks for tumors in your chest, belly or pelvis
* PET scan: Highlights areas with cancer
* Bone marrow biopsy: Checks if cancer is in the marrow
* Spinal tap (lumbar puncture): Looks for cancer cells in spinal fluid

#### **Stages of Burkitt lymphoma**

Healthcare providers use stages to show how far the cancer has spread:

* Stage I (1): One area or lymph node is affected.
* Stage II (2): Cancer is in two or more areas on the same side of your breathing muscle (diaphragm).
* Stage III (3): Cancer is on both sides of your diaphragm.
* Stage IV (4): Cancer has spread outside your lymph system (like to your liver, lungs or bone marrow).

## **Management and Treatment**

Because Burkitt lymphoma grows fast, treatment needs to start quickly. Options include:

* Chemotherapy: Main treatment, often intense and started right away
* Immunotherapy: Helps your immune system find and attack cancer
* Radiation therapy: Sometimes used with chemo, mostly for adults
* Stem cell transplant: May help if cancer returns after treatment
* Surgery: Used in rare cases, like when a tumor blocks your intestines

### **When to see a doctor**

Your provider will schedule regular follow-ups to monitor your health. These appointments may include blood tests and CT scans.

Call your provider if you or your child has:

* Chest pain or shortness of breath
* Fever over 100.4 degrees Fahrenheit (38 degrees Celsius)
* Nosebleeds or bleeding gums
* Pain that won’t go away
* Pale skin or easy bruising

## **Outlook / Prognosis**

Burkitt lymphoma is curable in many cases. It responds well to treatment, especially in kids and teens. Children tend to handle chemotherapy better than adults, who may have other health issues that can make treatment harder.

#### **Burkitt lymphoma survival rates**

While Burkitt lymphoma is aggressive, many people respond well to treatment. Here’s what the survival rates typically look like:

* Early-stage in kids: Over 90% survive long-term.
* Advanced-stage in kids: 80% to 90% survive.
* Adults: Over 50% go into remission with treatment.

These are only averages. Your outcome may be different, so talk to your provider for more personal details.

#### **Self-care tips**

Treatment can be tough, but there are ways to cope:

* Find support: Talking to others with similar experiences can help.
* Rest: Give yourself time to recover.
* Eat well: A dietitian can help you stay strong during treatment.
* Plan ahead: Ask your provider what to expect. Let loved ones support you.
* Support your child: A child life specialist can help kids deal with the emotional side of illness.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Burkitt lymphoma primarily includes other CD10 positive B-cell lymphomas: diffuse large B-cell lymphoma (DLBCL), high-grade B cell lymphoma, high-grade follicular lymphoma, and B-cell acute lymphoblastic leukemia/lymphoma (B-ALL). Both DLBCL and high-grade B cell lymphomas typically have larger cells with more pleomorphism than is expected with Burkitt lymphoma. BCL2 positivity and a Ki67 proliferation index <90% favor a diagnosis other than Burkitt lymphoma. Finding an *MYC* translocation is not diagnostic of Burkitt lymphoma; approximately 10% of DLBCL have an MYC translocation. B-ALL may resemble Burkitt lymphoma in size, but it typically has finer chromatin. By immunohistochemistry or flow cytometry, B-ALL will often express markers of immaturity, eg, CD34 and TdT.

Some uncommonly encountered entities should also be considered. Cases with Burkitt lymphoma-type morphology that lack an MYC translocation should be examined for abnormalities of chromosome 11q for the diagnosis of Burkitt-like lymphoma with 11q aberration. The prognosis for this recently described entity appears similar to that of Burkitt lymphoma.

**EPIDEMIOLOGY**

Burkitt lymphoma accounts for approximately 1% to 5% of all non-Hodgkin lymphomas.Burkitt lymphoma is more common in Caucasians than in persons of African or Asian descent. As with most types of lymphoma, Burkitt lymphoma is more prevalent in males, with a 3 to 4:1 male-to-female ratio.

The distribution of endemic cases of Burkitt lymphoma in Africa and Papua New Guinea corresponds to areas where malaria and Epstein-Barr virus are prevalent. In children younger than 18, the incidence is approximately 3 to 6 cases per 100,000 children annually. The average age of diagnosis is 6 years.

The sporadic form is localized to North America and Europe, with a median diagnosis age of 30 years. Sporadic Burkitt lymphoma has an annual estimated incidence of 4 per 1 million children younger than 16 years of age, whereas the incidence is 2.5 per 1 million in adults. The average age of diagnosis in pediatric patients is 3 to 12 years of age.

The immunodeficiency-associated variant has an incidence of 22 per 100,000 person-years in the United State

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### **Diffuse large B-cell lymphoma**

**Definition and description**

Diffuse large B-cell lymphoma, or DLBCL, is a blood cancer that involves changes in your B cells, a particular type of white blood cell (lymphocyte). It’s the most common form of aggressive non-Hodgkin lymphoma and a type of B-cell lymphoma.

DLBCL affects your lymphatic system. Your lymphatic system is a network of tissues, vessels and organs that help fight infection in your body. Normal B cells are a part of that infection-fighting network. But with DLBCL, healthy B cells change into fast-growing cancer cells that overtake healthy ones. They’re no longer able to fight off infection-causing invaders, like viruses and bacteria.

With diffuse large B-cell lymphoma, cancerous B cells may appear in your lymph nodes. But they may also appear in virtually any organ, including your gastrointestinal tract, thyroid, skin, breast, bone or brain.

Although it’s aggressive, DLBCL is often treatable and curable — especially with early diagnosis and treatment.

#### **Types of DLBCL**

The World Health Organization (WHO) has identified over a dozen different types of DLBCL. Each type’s unique traits tell healthcare providers how the cancer will likely progress and respond to treatment. The classifications depend on things like:

* Genetic changes. The genetic changes in the lymphoma cells are the most important identifier.
* The part of your body where DLBCL starts. For example, primary CNS lymphoma starts in your central nervous system (CNS). Primary mediastinal B-cell lymphoma starts in the center of your chest (mediastinum).
* If there’s an association with a virus. Some types of DLBCL happen in people with a specific virus. For example, people with EBV-positive DLBCL have an Epstein-Barr virus infection.

Understanding how the specific type of diffuse large B-cell lymphoma will impact your care journey is important, but the specifics can be confusing. Ask your provider to explain how your type of DLBCL will impact treatment options and outlook.Diffuse large B-cell lymphoma is the most common type of lymphoma. But as cancer diagnoses go, it’s still uncommon overall. According to the National Cancer Institute, in 2020, about 6 people in 100,000 received a DLBCL diagnosis. In comparison, about 500 people in 100,000 received a diagnosis of cancer affecting any part of their bodies.

## **Symptoms and Causes**

The symptoms most people notice with diffuse large B-cell lymphoma are swollen lymph nodes in their neck, armpits or groin. They usually appear as a lump that doesn’t go away and seems to be getting larger. The lump isn’t usually painful, but it can be.

About 30%of people with DLBCL have “B symptoms,” which include:

* A fever above 103 degrees Fahrenheit (39.5 degrees Celsius) that lasts longer than two days or comes and goes
* Unexplained weight loss that involves losing more than 10% of your body weight over six months
* Heavy night sweats (so intense that it drenches your sheets)

Having these symptoms doesn’t necessarily mean you have diffuse large B-cell lymphoma. That said, you should contact a healthcare provider anytime you notice changes in your body that last for several weeks.

### **Causes of diffuse large B-cell lymphoma**

Diffuse large B-cell lymphoma happens when B cells mutate (change). These are acquired genetic mutations, meaning you develop them during your lifetime instead of being born with them.

#### **Risk factors**

Medical researchers aren’t sure what triggers the mutations in DLBCL, but they’ve identified several factors that may increase your risk. Risk factors for diffuse large B-cell lymphoma include:

* Age. Most people diagnosed with DLBCL are in their 60s. The average age of diagnosis is 64 years old.
* Sex. DLBCL is slightly more common in males.
* Race. DLBCL affects more people who are white than people who are Black.
* Family history of DLBCL. The genetic mutations in DLBCL aren’t hereditary, which means, they don’t run in families. Still, studies show you’re at a slightly higher risk if a first-degree biological relative (parent, sibling or child) also has DLBCL. Medical researchers aren’t sure why.
* Infections. Viral infections associated with DLBCL include Epstein-Barr virus, human immunodeficiency virus (HIV) and hepatitis B and C.
* Weakened immune system. Having a condition that impacts your immune system is the most significant risk factor for DLBCL. Examples include having a primary immunodeficiency or autoimmune disorder, or taking immunosuppressants after an organ transplant.
* Increased body mass index (BMI) in young adults. The risk is especially high for young adults with obesity that persists throughout adulthood.
* Exposure to toxic substances. Exposure to pesticides used in farming and certain chemicals used in manufacturing may increase your risk.

## **Diagnosis and Tests**

Healthcare providers diagnose DLBCL with a lymph node biopsy. This procedure removes all or part of a lymph node to check it for cancer cells. They also do genetic testing to learn which cell mutations are involved.

If you do have DLBCL, your provider may order additional tests to learn more about it, including whether it’s spread beyond your primary lymph node. Tests include:

* Blood tests. These include a complete blood count (CBC) to check your general health and tests that detect viruses, like HIV, EBV and hepatitis B and C.
* Lactate dehydrogenase (LDH) test. This test checks the level of LDH (an enzyme) in your body fluid. Over 50% of people with DLBCL have high levels.
* Imaging tests. You may need a CT scan, MRI or PET scan to show whether the cancer has spread throughout your body.
* Bone marrow biopsy. This test checks for lymphoma cells in your bone marrow.
* Lumbar puncture. This test checks for lymphoma cells in the fluid surrounding your spinal cord.

#### **Stages of diffuse large B-cell lymphoma**

Healthcare providers use cancer staging systems to determine how advanced the cancer is. This helps them develop treatment plans and estimate prognosis, or expected outcome. The stages of DLBCL are:

* Stage I: The cancer is in one lymph node, one lymph organ (thymus, spleen and tonsils) or in just one area of a single organ outside of your lymph system.
* Stage II: This is when there’s lymphoma in two or more lymph node groupings or lymph node organs on the same side of your diaphragm.
* Stage III: This stage is when there’s cancer in lymph nodes or lymph tissue on both sides of your diaphragm.
* Stage IV: DLBCL has spread to organs outside of your lymph system, like your bone marrow, liver or lungs.

Your provider may refer to stage I and II DLBCL as “early stage” and stage III and IV DLBCL as “advanced stage.”

## **Management and Treatment**

One of the most common treatments for diffuse large B-cell lymphoma is R-CHOP. It combines the monoclonal antibody drug rituximab with three chemotherapy drugs and a corticosteroid.

This treatment is safe and effective but doesn’t always work or keep DLBCL from coming back (recurring). Studies show relapses or recurrent cancer affect an estimated 30% to 40% of people with DLBCL who receive R-CHOP. If that happens, your provider may recommend the following treatments:

* Second-line therapy and autologous stem cell transplant. Second-line therapy is intensive treatment with combined cancer drugs.
* CAR T-cell therapy. This treatment is a type of immunotherapy that helps your T cells (a type of white blood cell) fight cancer more effectively.
* Targeted therapy. This treatment targets the genetic changes or mutations that cause diffuse large B-cell lymphoma.

## **Outlook / Prognosis**

While some DLBCL can be life-threatening and difficult to treat, healthcare providers can often cure it using a combination of cancer drugs. Often, front-line or initial treatment sends DLBCL into complete remission. This means there are no signs and symptoms of cancer. Front-line treatment cures about 60% of people with DLBCL. In general, people who are cancer-free two years after their diagnosis can expect to live as long as most people in their age group.

According to the National Cancer Institute, 64.7% of all people with DLBCL are alive five years after diagnosis. Like many kinds of cancer, survival rates increase for people with early-stage cancer.

Still, while cure rates and survival rates may be helpful, your experience depends on many factors, including the type of DLBCL, cancer stage and your overall health. These are factors that only your healthcare provider knows about. Your provider is your best resource for answering questions about what to expect.

## **Prevention**

There’s no guaranteed way to prevent DLBCL and nothing you can do about risk factors you can’t control, like having an immunodeficiency. But you can take steps to reduce your risk of developing certain infections linked to DLBCL, like hepatitis and HIV. You can also work to maintain a BMI (body mass index) that’s healthy for you.

## **Living With**

It can be stressful and exhausting to live with any form of cancer, including diffuse large B-cell lymphoma. It’s important that you do what you can to take care of yourself throughout DLBCL treatment. Here are some suggestions:

* Focus on nutrition. Know what foods to eat and avoid, so you’re nourishing your body.
* Rest. Fatigue is the most common side effect of DLBCL treatment. Get as much rest as you can.
* Develop an exercise routine. Gentle exercise may help you cope with stress.
* Find support. Diffuse large B-cell lymphoma is a rare condition. You may feel as if no one understands what you’re going through. Connecting with people who are in your situation may help.

### **When should I see a doctor?**

You’ll see your healthcare provider throughout your treatment. They’ll monitor your health and check how the treatment is working.

Afterward, you may see your provider every three to four months for the first two years and then less frequently for the next three years. That’s because diffuse large B-cell lymphoma may come back. Contact your healthcare provider if you notice changes in your body that may mean the cancer has recurred.

**Differential Diagnosis**

The differential diagnoses include infectious mononucleosis, Hodgkin lymphoma, T-cell lymphomas, and other large cell malignancies such as carcinomas, melanoma, and Kikuchi disease. Melanomas can also involve the lymph nodes but can be differentiated from DLBCL by positive S100, HMB-45, and Melan A staining.

**EPIDEMIOLOGY**

The incidence of non-Hodgkin lymphoma in the United States is approximately 7 cases per 100,000 per year. DLBCL accounts for about 25% of all NHL cases worldwide. DLBCL is the most common NHL, followed by FL. The disease occurs more frequently in whites, followed by African Americans and Asians with male preponderance and a median age of 64 years. The overall incidence increases exponentially with age.

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### **Follicular lymphoma**

**Definition and description**

Follicular lymphoma is a very slow-growing cancer that may appear in your lymph nodes, your bone marrow and other organs. You can have follicular lymphoma without having symptoms. Healthcare providers consider follicular lymphoma a chronic illness. There are ways to treat follicular lymphoma, but the condition often comes back. Healthcare providers are hopeful newer treatments may mean a cure for follicular lymphoma is on the horizon.

#### **How does follicular lymphoma affect my body?**

Follicular lymphoma is a subtype of B-cell lymphoma, a form of non-Hodgkin’s lymphoma. Follicular lymphoma symptoms mirror non-Hodgkin lymphoma symptoms, such as swollen lymph nodes, fever and drenching night sweats.

But many people are diagnosed with follicular lymphoma before they develop symptoms. People who’re in good health and don’t have symptoms may not need immediate treatment. Healthcare providers may recommend watchful waiting. In watchful waiting, healthcare providers monitor your overall health and symptoms.

Follicular lymphoma may affect your emotional well-being long before it affects your physical well-being. A recent study showed people with follicular lymphoma and other slow-growing lymphomas struggle with anxiety because they don’t know if they’ll develop symptoms or need to start treatment.

#### **Is follicular lymphoma a serious illness?**

Yes, follicular lymphoma can be a serious and challenging illness. Here’s why:

* Transformation: Follicular lymphoma can change or transform into diffuse large B-cell lymphoma (DLBCL). This is a more aggressive cancer that typically causes new and more significant symptoms, including spreading cancer into other areas of your body. About 3 % of people who have follicular lymphoma develop DLBCL.
* Relapse: Follicular lymphoma symptoms often subside after treatment and then come back. This cycle of remission-relapse-remission means people who have follicular lymphoma feel as if they’re never able to say they’re “done” with treatment.

## **signs and symptoms of follicular lymphoma**

General symptoms may include:

* Painless swelling in your neck, armpit or groin caused by enlarged lymph nodes.
* Fever that infection or other illness is causing.
* Weight loss with no known cause, particularly losing 10% or more of your weight within the past six months.
* Sweating and chills. Drenching night sweats and chills that won't go away may be a sign of illness, including follicular lymphoma.
* Fatigue. This is an ongoing sense of feeling so tired that you can’t manage your daily activities.

### **causes of follicular lymphoma**

Researchers don’t know all of the factors that cause follicular lymphoma. They do know changes in people’s chromosomes cause about 85% of cases. The changes allow unhealthy or cancerous cells to multiply and grow.

## **Diagnosis and Tests**

Healthcare providers may use several tests to diagnose follicular lymphoma:

* Biopsy: Healthcare providers may take lymph node tissue samples to test for signs of cancer.
* Positron emission tomography (PET) scans: Healthcare providers use this test to observe cancer cell activity and establish a cancer grade.
* Computed tomography (CT) scan: This test helps healthcare providers monitor cancer and evaluate treatment response.

### **stages of follicular lymphoma**

Healthcare providers establish cancer stages so they know what kind of treatment may be best to treat the cancer. Follicular lymphoma stages range from I to IV:

* Stage I: Cancer is found in one or more lymph nodes. Healthcare providers diagnose about 25% of all follicular lymphoma cases at this stage.
* Stage II: Cancer is found in lymph nodes above or below your diaphragm. Healthcare providers diagnose about 15% of all follicular lymphoma cases at this stage.
* Stage III: Cancer is found in lymph nodes on both sides of your diaphragm. Healthcare providers diagnose about 26% of all follicular lymphoma cases at this stage.
* Stage IV: Cancer has spread outside of the lymph nodes to bone marrow and/other organ systems. Healthcare providers diagnose about 27% of all follicular lymphoma at this stage.

## **Management and Treatment**

Healthcare providers may use a combination of watchful waiting and therapy to treat follicular lymphoma. Here’s more information about each potential treatment:

* Watchful waiting or active surveillance: If your healthcare provider recommends watchful waiting, you’ll have regular appointments so they can do physical examinations, laboratory tests and imaging tests.
* Radiation therapy: Healthcare providers may use radiation therapy to treat early-stage follicular lymphoma.
* Monoclonal antibody therapy: Healthcare providers use lab-created antibodies designed to find and kill specific cancer cells.
* Chemotherapy: Healthcare providers may use chemotherapy alone or combine chemotherapy with other treatments.
* Targeted therapy: Targeted therapy uses drugs or other substances to attack cancer cells without hurting normal cells.
* Immunotherapy: Immunotherapy stimulates your immune system. Treatments can fuel your body’s production of cancer-fighting cells or help healthy cells identify and attack cancer cells.
* Bone marrow/stem cell transplantation: Healthcare providers may recommend this treatment if follicular lymphoma comes back after chemotherapy.

## **Outlook / Prognosis**

Follicular lymphoma is a slow-growing condition that’s considered a chronic illness. Studies show about half of all people diagnosed with follicular lymphoma are alive nearly 20 years after diagnosis. About 90% of people are alive five years after diagnosis.

## **Prevention of follicular lymphoma**

Unfortunately, researchers haven’t identified ways to reduce the risk of developing this condition. If you’re concerned you may be at risk, ask your healthcare provider to review your medical history, including your family medical history.

## **Living With**

Self-care is an important part of living with cancer. Self-care suggestions include:

* Establish good eating and exercise habits. Ask to speak with a nutritionist for healthy menu ideas.
* Fatigue is a common symptom and treatment side effect. Pay attention to your body and rest when you need to rest, not just when you can.
* You may be living with cancer for a long time. That’s good news of course, but chronic illness may be challenging. Talking to a therapist or finding a support group may help you navigate the challenges.

### **When should I see a doctor?**

If you’ve been diagnosed with follicular lymphoma, your healthcare provider will set a schedule of follow-up appointments to monitor your condition and/or your treatment. But you should contact your healthcare provider as soon as possible if you notice changes in your body that may be signs of follicular lymphoma symptoms.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of follicular lymphoma (FL) includes a variety of lymphoid neoplasms and reactive conditions that can mimic its clinical, histologic, and immunophenotypic features. Accurate distinction is crucial for prognosis and treatment.

Reactive Follicular Hyperplasia

* Benign lymph node enlargement with preserved architecture.
* Follicles vary in size and shape, with polarization into light and dark zones and abundant tingible body macrophages.
* No monoclonality or t(14;18) translocation.
* Lack of BCL2 expression in germinal centers (usually BCL2-negative).
* No follicular dendritic cell (FDC) meshwork disruption.

## Diffuse Large B-Cell Lymphoma (DLBCL)

* Aggressive lymphoma that may arise de novo or via transformation from FL (especially grade 3 FL with diffuse areas).
* Shows sheets of large cells, loss of follicular pattern.
* Requires different treatment; FL with areas of DLBCL should be treated as DLBCL.

## Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)

* Contains “popcorn” or lymphocyte-predominant (LP) cells, positive for CD20 but negative for CD30 and CD15.
* Different clinical behavior and immunophenotype from FL.

## Mantle Cell Lymphoma (MCL)

* Typically expresses cyclin D1 and SOX11, negative for CD10 and BCL6.
* Usually lacks follicular pattern.
* Can be distinguished by immunohistochemistry and genetic studies (t(11;14)).

## Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

* Usually extranodal, with marginal zone B-cell phenotype.
* Negative for CD10 and BCL6, positive for CD20.
* Lacks t(14;18) translocation.

## Lymphoplasmacytic Lymphoma (e.g., Waldenström Macroglobulinemia)

* Characterized by plasmacytoid differentiation and IgM paraprotein.
* Different immunophenotype and clinical presentation.

## Progressive Transformation of Germinal Centers (PTGC)

* Benign condition with enlarged follicles, may mimic FL floral variant.
* No monoclonality or BCL2 rearrangement.

## Castleman Disease (Hyaline Vascular Variant)

* Shows prominent follicular dendritic cells and vascular proliferation.
* Lacks monoclonal B-cell proliferation.

**Epidemiology of Follicular Lymphoma (FL)**:

* Incidence:
  + FL is the second most common subtype of non-Hodgkin lymphoma (NHL) in the United States and Western countries, accounting for about 20–40% of all NHL cases in these regions.
  + The age-standardized incidence rate in high-income countries is approximately 2.4 to 3 per 100,000 persons per year.
  + Some sources report an incidence of about 6 new cases per 100,000 persons per year in the US, reflecting variations in data sources and population.
  + Incidence is generally lower in Eastern Europe, Asia, and developing countries, about threefold less than in Western populations.
* Prevalence and Trends:
  + The prevalence of FL is increasing, partly due to improved survival and aging populations.
  + In the US and Western Europe, the 20-year prevalence of FL has increased by approximately 5% (US) and 12% (Western Europe) between 2020 and 2025.
  + Global data show a rising burden of lymphoma subtypes including FL, especially in low and middle socio-demographic index (SDI) regions, while some high SDI regions show stable or modest declines.
* Demographics:
  + FL primarily affects adults with a median age at diagnosis around 60 years.
  + There is a slight female predominance in some populations, though data vary.
  + The disease is rare in children.
* Geographic Variation:
  + FL is most common in North America and Western Europe.
  + Lower incidence rates are observed in Eastern Europe, Asia, and developing countries.
  + Regional increases in NHL, including FL, have been noted in South America (e.g., Colombia, Chile), parts of Eastern Europe, and Central Asia.
* Risk Factors:
  + Exposure to pesticides and herbicides has been linked to increased FL risk.
  + Aging population and improved diagnostic techniques contribute to rising incidence.
* Mortality:
  + FL is generally an indolent lymphoma with favorable prognosis; death rates are lower compared to aggressive NHL subtypes.
  + Death rate reported as approximately 0.4 per 100,000 persons per year in the US.

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## **Mantle Cell Lymphoma**

**Definition and description**

Mantle cell lymphoma (MCL) is a rare blood cancer that starts in your lymphocytes (a type of white blood cell). It’s a subtype of non-Hodgkin lymphoma.

In most cases, MCL begins as a slow-growing cancer that later grows rapidly. It spreads throughout your lymphatic system. In its advanced stages, the cancer spreads from your lymph nodes to other areas, like your bloodstream, bone marrow and digestive system.

With mantle cell lymphoma, you might have periods of remission followed by periods of recurrence. That means the cancer can go away and come back, often several times. Treatment can’t cure MCL, but it can lengthen the amount of time you’re in remission.

Mantle cell lymphoma is rare, affecting about 1 in 200,000 people. Anyone can develop this type of cancer. People between the ages of 60 and 70 have a slightly higher risk.

### **Types of mantle cell lymphoma**

The two types of mantle cell lymphoma are:

* Classical MCL. This type starts in your lymph nodes but usually spreads to other areas of your body. It’s usually more aggressive (fast-growing). Most MCL cases are the classical type.
* Leukaemic non-nodal MCL. This type usually causes a swollen spleen and lymphoma cells in your blood and bone marrow. It tends to grow more slowly than the classical type.

## **Symptoms and Causes**

MCL symptoms vary from person to person and can look like ordinary illnesses. They may not always appear to be cancer-related. That’s one reason why mantle cell lymphoma is usually in the later stages at the time of diagnosis.

You might not have any symptoms with MCL. But if you do, they might include:

* Bruising
* Headaches
* Fatigue
* Fever
* Indigestion
* Loss of appetite
* Night sweats
* Swollen lymph nodes
* Weakness
* Unexplained weight loss

### **Causes of mantle cell lymphoma**

Most of the time, mantle cell lymphoma happens when certain genes mutate (or change) and alter how your B cells function. Researchers don’t know what triggers this genetic change, but here’s how it works:

1. Abnormal B cells make too much cyclin D1 (a protein that helps B cells grow).
2. The cyclin D1 overload makes B cells duplicate and multiply uncontrollably.
3. The duplicate cells make tumors.

### **complications of mantle cell lymphoma**

As mantle cell lymphoma progresses, you might develop complications like:

* Gastrointestinal bleeding
* Ruptured spleen
* Tumor lysis syndrome

## **Diagnosis and Tests**

Your healthcare provider may use many different tests to diagnose MCL, including:

* Lab tests. These may include a complete blood count (CBC), comprehensive metabolic panel (CMP), LDH test or a uric acid level test.
* Biopsies. Your healthcare provider may also recommend a lymph node biopsy or bone marrow biopsy. These procedures can help confirm the presence of cancer cells. Once a provider takes a tissue sample, they’ll send it to a pathologist for testing.
* Imaging tests. Your provider might take imaging tests to determine how far the cancer has spread. Depending on the location of the cancer, you might need a colonoscopy, CT scan, EGD (esophagogastroduodenoscopy) or PET scan.

Healthcare providers usually suspect mantle cell lymphoma after routine blood work shows a high lymphocyte count. If your lab results are abnormal, a healthcare provider will do an exam and ask you to describe your symptoms. They might gently press around your lymph nodes to see if they’re swollen.

### **stages of mantle cell lymphoma**

Healthcare providers use a disease-specific staging system called the Mantle Cell Lymphoma International Prognostic Index (MIPI). It helps them predict survival rates. In general, late-stage MCL is more likely to come back than early-stage MCL.

Healthcare providers determine cancer stage by finding out how far the cancer has spread:

* Stage I. Localized to one lymph node or cluster of lymph nodes in the same area.
* Stage II. Cancer is in two or more lymph nodes or lymph node clusters on the same side of your diaphragm.
* Stage III. MCL has spread to both sides of your diaphragm. Or it’s in the lymph nodes in your spleen and above your diaphragm.
* Stage IV. Mantle cell lymphoma has spread to distant areas of your body or parts that aren’t lymph nodes.

## **Management and Treatment**

MCL treatment is different for everyone. The option that’s right for you depends on factors like tumor location and growth.

Treatments for mantle cell lymphoma include:

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

You might qualify for some treatments but not others.

If you have MCL, you may want to consider a clinical trial. Clinical trials test new ways to treat cancer. The new treatments might not cure mantle cell lymphoma, but they may give you more symptom-free time to enjoy life. Ask your healthcare provider if you could be a candidate.

## **Outlook / Prognosi**

Mantle cell lymphoma isn’t a curable lymphoma. But there are treatments that can send it into remission.

Cancer in remission isn’t the same as cancer that’s been cured. Mantle cell lymphoma can come back (relapse) after being in remission for months or years.

The amount of time you experience remission may be shorter with MCL. But newer targeted treatments can increase the remission period. To learn more about your mantle cell lymphoma prognosis, ask your healthcare provider.

#### **Survival rate**

The five-year survival rate for mantle cell lymphoma is about 50%. That means around half of the people diagnosed with this disease are still alive five years after diagnosis.

Survival rates are just estimates. They can’t tell you how long you’ll live or how you’ll respond to a particular treatment. To learn what survival rates mean for you, talk to your healthcare provider.

## **Prevention**

You can’t prevent MCL. If you receive a diagnosis, it doesn’t mean you’ve done something wrong. Researchers are learning more about why genes mutate or change within our bodies to create cancers like MCL.

## **Living With**

Taking care of yourself — physically, emotionally and mentally — is essential with mantle cell lymphoma.

Here are some suggestions that might help:

* Acknowledge your emotions. Ignoring negative feelings won’t make them go away. Honoring your emotions is the first step in finding the support you need.
* Get support. Joining a support group is a great way to find others who are going through similar situations. Ask your healthcare provider about local or online resources.
* Manage your stress. Find ways to relax and bring intention into your daily life. Try meditation or other mindfulness exercises.
* Stick to a routine. The cycle of remission and relapse can make you feel out of sorts. Finding a daily routine and sticking to it can help you regain control.
* Talk to a counselor. It’s important to take care of your mental health. A counselor or therapist can help you sort through complicated emotions.

### **When should I see my healthcare provider?**

If you’re receiving treatment for mantle cell lymphoma, you’ll see your healthcare provider regularly. They’ll monitor your progress and help you manage side effects.

If your condition is in remission, you’ll have occasional follow-ups. Ask your provider how frequently to schedule these appointments.

**Epidemiology of Mantle Cell Lymphoma (MCL)**:

Incidence:

* + MCL is a relatively uncommon subtype of non-Hodgkin lymphoma (NHL), comprising approximately 3–10% of all NHL cases.
  + The annual incidence is estimated at about 0.5 to 1 case per 100,000 population globally, with slight regional variations.
  + SEER data from the United States indicate an increase in incidence from 0.711 per 100,000 (2000–2006) to 0.800 per 100,000 (2007–2013), largely driven by cases in patients aged 65 years and older.
  + Recent trends (2015–2019) suggest a slight decline in incidence (~0.49% annual decrease), following an earlier period of increase.
* Demographics:
  + MCL predominantly affects older adults, with a median age at diagnosis around 68 years.
  + Most cases occur in patients aged 65–74 years.
  + There is a male predominance, with a male-to-female ratio of approximately 1.46:1.
  + Whites have a higher risk compared to Blacks, Hispanics, and Asian Americans.
* Survival Trends:
  + Relative 5-year survival rates have modestly improved over time, particularly in patients aged 50–64 years (from 61.3% to 67.4%) and those with advanced (stage IV) disease (from 48.0% to 55.1%).
  + Despite improvements, MCL remains an aggressive lymphoma with poorer prognosis compared to many other NHL subtypes.
* Geographic and Global Trends:
  + Exact global prevalence is difficult to determine due to variability in diagnostic criteria and reporting.
  + Incidence and burden of NHL, including MCL, are rising in some regions such as South America (Chile, Colombia), parts of Eastern Europe, and Central Asia.
  + Conversely, some high-income regions (North America, Western Europe, parts of Asia) have stable or slightly declining incidence rates.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis primarily includes SLL/CLL and DLBCL. Both SLL/CLL and mantle cell lymphoma are CD5-positive, mature B-cell lymphomas and may be difficult to distinguish by flow cytometry alone. When there is positivity for CD200 and CD23, the diagnosis is most likely SLL/CLL. Mantle cell lymphoma is typically negative for CD23; it is positive for FMC7. Confirmation of MCL is typically performed by either FISH for t(11;14) or immunohistochemistry for cyclin D1 and/or SOX11. In tissue, uniform positive immunohistochemical expression of B-cells by Cyclin D1 and SOX 11 supports MCL. Focal positivity for Cyclin D1 may be seen in the proliferation centers of SLL/CLL and should not prompt a diagnosis of MCL. Diffuse large B-cell lymphoma is entertained when large cell proliferation is negative for Cyclin D1 and SOX11.

When the architecture of a lymph node is intact and only shows focal involvement by atypical cyclin D1 positive cells, mantle cell neoplasia in situ may be a diagnostic consideration.

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### **Marginal zone lymphoma**

**Definition and description**

Marginal zone lymphoma (MZL) refers to a group of rare, slow-growing non-Hodgkin lymphomas. They typically develop in lymphoid tissue. This tissue contains B cells, a type of white blood cell that’s in parts of your immune system like your lymph nodes and spleen.

Your lymph nodes contain lymphoid follicles. Lymphoid follicles have two zones, or sections — mantle zones and marginal zones. Marginal zones wrap around mantle zones. Marginal zone lymphoma happens when B cells in the marginal zone mutate (change), becoming abnormal cells that multiply excessively.

Marginal zone lymphomas usually affect people aged 60 and older. They tend to be more common in men than in women.

#### **What are marginal cell lymphoma types?**

There are three types of marginal zone lymphomas:

* Mucosa-assisted lymphoid tissue (MALT) lymphoma: This is the most common type of MZL. Healthcare providers may use the term “extranodal marginal cell lymphoma.” This type of marginal zone lymphoma may develop in the lining of your belly (gastric MALT) or in your lungs, skin, thyroid, salivary gland, bowels or near your eye (non-gastric MALT).
* Nodal marginal zone lymphoma: This type affects your lymph nodes but can appear in your bone marrow.
* Splenic marginal zone lymphoma: This rare type of marginal zone lymphoma affects your spleen, blood and bone marrow.

## **Symptoms and Causes**

Marginal zone lymphoma typically grows very slowly. You may have this condition without having symptoms. Symptoms vary depending on the condition type. In general, marginal zone lymphomas cause the following symptoms:

* Fever.
* Night sweats.
* Unexplained weight loss.

#### **MALT lymphoma symptoms**

Extranodal marginal zone lymphoma symptoms vary based on the lymphoma location. For example, MALT lymphoma in your belly may cause:

* Nausea and vomiting.
* Belly pain.
* Feeling full even when you haven’t eaten.

Non-gastric MALT symptoms may include changes in your eye’s surface (conjunctiva) or tear (lacrimal) glands.

#### **Nodal marginal zone lymphoma symptoms**

Nodal marginal zone lymphoma symptoms may include:

* Fever.
* Night sweats.
* Unexplained weight loss.

#### **Splenic marginal zone lymphoma symptoms**

Splenic marginal zone lymphoma symptoms may include:

* Fatigue.
* Enlarged spleen.
* Night sweats.
* Unexplained weight loss.

### **Causes of marginal zone lymphoma**

In general, people with marginal zone lymphoma have a family history of lymphoma, frequent infections or autoimmune diseases. The subtypes have specific causes:

* MALT lymphoma causes include bacterial infections, specifically *H. pylori* infections, autoimmune diseases like Hashimoto’s disease or Sjӧgren’s syndrome, or having a family history of lymphoma.
* Splenic marginal zone lymphoma is linked to hepatitis C and autoimmune diseases.
* Nodal marginal zone lymphoma is associated with hepatitis C.

#### **marginal zone lymphoma risk factors**

Risk factors include having a family history of lymphoma and having certain infections and autoimmune disorders.

## **Diagnosis and Tests**

Healthcare providers diagnose the condition by asking questions about your symptoms, your medical history and your family medical history.

#### **What tests do providers use to diagnose marginal zone lymphoma?**

Tests vary based on the sub-type. In general, tests may include:

* CBC.
* LDH test.
* Beta-2 microglobulin, a tumor marker for blood cancers.
* Liver function tests.
* Renal (kidney) function tests.
* Serum protein immunofixation (IFX). This test checks for changes in your blood.
* Certain bacterial and viral infections like *H. pylori*, hepatitis C and hepatitis.
* CT scan.
* Needle biopsy.
* Bone marrow biopsy.
* Biopsy to obtain samples of cells or tissue from various parts of your body.

#### **MZL stages**

Healthcare providers use cancer staging systems to plan treatment and develop prognoses. MZL stages are:

* Stage I: Cancer in one lymphatic area.
* Stage II: Cancer in two more lymph nodes located above or below your diaphragm.
* Stage II: Cancer in several lymph nodes above and below your diaphragm.
* Stage IV: Cancer that has spread to multiple organs.

## **Management and Treatment**

Marginal zone lymphoma grows very slowly. People with this condition may not need immediate treatment. Healthcare providers instead may monitor people’s health until they determine that treatment is necessary. This is “watchful waiting” or active surveillance.

Treatments for MZL vary depending on the subtype but may include:

* Antibiotics to treat bacterial infections, specifically *H. pylori*.
* Chemotherapy.
* Radiation therapy.

## **Outlook / Prognosis**

That depends on the condition type. For example, antibiotic treatment that eliminates *H. pylori* may cure extranodal marginal zone lymphoma. Other treatments put the condition into remission. Remission happens when cancer treatment eliminates symptoms and tests show no signs of disease. But marginal zone lymphoma may recur (come back) after treatment.

#### **What is the survival rate for marginal zone lymphoma?**

Survival rates vary based on the type of marginal zone lymphoma. One study suggests the following:

* An estimated 88% of people with extranodal marginal zone lymphoma were alive five years after diagnosis.
* An estimated 79% of people with splenic marginal zone lymphoma were alive five years after diagnosis.
* An estimated 76.5% of people with nodal marginal zone lymphoma were alive five years after diagnosis.

When you think about survival rates, it’s important to remember these are estimates based on other people’s experiences and data collected over time. Your experience may be different.

Marginal zone lymphoma affects people aged 60 and older. In many cases, people with this condition ultimately die from causes other than marginal zone lymphoma.

If you have marginal zone lymphoma, your healthcare provider is your best resource for information about your prognosis.

## **Prevention**

This condition happens for several reasons, including autoimmune diseases and genetic issues you can’t control.

## **Living With**

If you’ve been diagnosed with marginal zone lymphoma, contact your provider if:

* You notice changes in your body that may be marginal zone lymphoma symptoms.
* You’re getting treatment and your symptoms get worse.
* You’re in remission, and notice changes that could indicate your condition is coming back (recurring).

#### **What can I do to take care of myself?**

Self-care is an important part of living with lymphoma, including rare lymphomas such as marginal zone lymphoma. Here are some steps you can take:

* Manage your stress. If you have marginal zone lymphoma, you may not have symptoms that require treatment. While that’s good news, it can be stressful wondering if you’ll have symptoms. Exercise, listening to music or activities like yoga may help.
* Drink enough fluids. Cancer treatment and side effects may cause dehydration.
* Eat a well-balanced diet. Focus on small meals that include fruit, vegetables, nuts and full-fat dairy products.

## **Incidence and epidemiology**

MZLs represent approximately 5%–15% of all non-Hodgkin lymphomas in the Western world. EMZLs comprise approximately two-thirds and can arise at any extranodal site, usually in the context of chronic antigenic stimulation due either to infections or autoimmune disorders. The stomach is the most common site, followed by ocular adnexa, lung and salivary glands. SMZL accounts for 20% and NMZL for <10% of cases. Aetiological heterogeneity is apparent across the anatomical sites, probably influenced by either intrinsic genetic/molecular characteristics or geographical factors and environmental exposures. Overall, the incidence appears to have increased in the last two decades (possibly because of improved pathological diagnosis), despite a decline in the incidence of *Helicobacter pylori*-associated gastric MZLs.

**Differential Diagnosis of Marginal Zone Lymphoma (MZL)**

Marginal zone lymphoma (MZL) comprises three main subtypes—splenic (SMZL), nodal (NMZL), and extranodal (MALT lymphoma)—each with overlapping but distinct clinical, morphological, immunophenotypic, and molecular features.

Splenic Marginal Zone Lymphoma (SMZL)

* Differential diagnoses:
  + Splenic red pulp diffuses small B-cell lymphoma (SRPL): Overlaps clinically and morphologically with SMZL; both present with splenomegaly and bone marrow involvement.
  + Lymphoplasmacytic lymphoma (LPL): Presence of monoclonal IgM paraprotein, bone marrow involvement, and MYD88 mutation (common in LPL, rare in SMZL).
  + Follicular lymphoma (FL): May involve spleen; distinguished by t(14;18) translocation and CD10/BCL6 positivity.
* Diagnostic tools: Peripheral blood and bone marrow examination, IHC markers (MNDA, IRTA1, T-Bet), and molecular markers (NOTCH2, KLF2 mutations).

Nodal Marginal Zone Lymphoma (NMZL)

* Differential diagnoses:
  + Extranodal MZL (EMZL): Occasionally involves lymph nodes; clinical and radiologic correlation needed.
  + SMZL: Must exclude splenic involvement to confirm NMZL.
  + LPL: Partial lymph node architecture preservation, plasmacytoid cells, Dutcher bodies, and MYD88 mutation.
  + Follicular lymphoma with marginal zone differentiation: FL cells are CD10+, BCL6+, and BCL2+, whereas NMZL cells are usually negative for CD10/BCL6 but positive for MNDA and IRTA1.
  + Small lymphocytic lymphoma (SLL): Different immunophenotype (CD5+, CD23+).
  + Reactive marginal zone hyperplasia: Polyclonal expansion, no clonal B-cell population.
* Diagnostic approach: Morphology, IHC panel (CD20, CD10, BCL6, MNDA, IRTA1), molecular studies (PTPRD mutations in NMZL), and clinical correlation.

Extranodal Marginal Zone Lymphoma (MALT lymphoma)

* Differential diagnoses:
  + Reactive lymphoid hyperplasia or pseudolymphoma: Polyclonal, lacks clonal rearrangements.
  + Other low-grade B-cell lymphomas: Such as follicular lymphoma or lymphoplasmacytic lymphoma depending on site and features.
  + Chronic inflammatory or infectious conditions: May mimic MALT lymphoma histologically.
* Diagnosis: Requires biopsy with IHC (CD20+, CD5−, CD10−), molecular studies, and clinical context (e.g., association with *Helicobacter pylori* in gastric MALT lymphoma).

Cutaneous Marginal Zone Lymphoma (CMZL)

* Differential diagnoses:
  + Cutaneous pseudolymphoma, arthropod bites, urticaria, leukemia cutis, basal cell carcinoma: Clinical and histologic correlation essential.
* Diagnosis: Skin biopsy showing dermal infiltration of small to medium B cells, IHC positive for CD20, CD79a, BCL-2, negative for CD10 and BCL-6.

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### **peripheral T-cell lymphoma (PTCL)**

**Definition and description**

Peripheral T-cell lymphoma (PTCL) isn’t a single disease. The term refers to a group of aggressive (fast growing) blood cancers that affect your lymphatic system and may spread (metastasize) to other areas of your body. Peripheral T-cell lymphomas are a form of non-Hodgkin lymphoma. They can affect nearly every part of your body and cause many different symptoms. Healthcare providers can successfully treat most subtypes, but the conditions often come back (recur). Medical researchers are studying potential treatments that may help people to live longer with PTCL.

#### **Are peripheral T-cell lymphomas common?**

No, they aren’t. One global study concluded PTCLs effect 2 in 100,000 people worldwide, and they make up about 10% of cases of non-Hodgkin lymphoma. The lymphomas are more common in Asia, Africa and the Caribbean than in the United States. They typically affect people ages 60 and older, but children and young adults may develop certain types of these lymphomas.

**types of peripheral T-cell lymphoma**

The World Health Organization (WHO) recognizes more than 20 PTCL subtypes. Nearly all PTCL subtypes have distinct genetic markers and other characteristics. According to one global study, the most common PTCL subtypes are:

* **Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS**):This is the most common subtype. PTCL isn’t a specifically defined subtype. Instead, it’s a group of conditions that represent cases that don’t fit well into one of the more specifically defined subtypes. Approximately 30% of all peripheral T-cell lymphoma cases are PTCL-NOS. This subtype affects your lymph nodes, bone marrow, spleen or liver.
* **Angioimmunoblastic T-cell lymphoma (AITL)**: This subtype represents between 15% and 30% of PTCL cases worldwide. It affects your lymph nodes, bone marrow, spleen or liver.
* **Anaplastic large cell lymphoma (ALCL)**: There are different forms of ALCL. They include primary cutaneous ALCL, which affects your skin. Another type, systemic ALCL, affects your lymph nodes, skin and other organs. Some cases of systemic ALCL are further categorized by changes in a specific gene, called anaplastic lymphoma kinase (ALK). ALCL represents approximately 15% of PTCLs.
* **Extranodal natural killer/T-cell lymphoma, nasal type**: This PTCL subtype commonly grows in the tissues of your nose, sinus cavities and upper throat, but it may also spread to your skin, digestive tract and other organs. Approximately 10% of PTCLs are this subtype.
* Intestinal T-cell lymphomas, which account for about 6% of PTCLs. This subtype affects your digestive system and includes enteropathy-associated T-cell lymphoma (EATL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).
* Adult T-cell lymphoma/leukemia, which may affect your skin and bones. There are four subtypes of ATLL: acute, lymphoma, chronic and smoldering. Acute and lymphoma subtypes are aggressive (fast growing) forms of ATLL. Chronic and smoldering are less aggressive. Each ATLL subtype affects different areas of your body.

## **Symptoms and Causes**

While each PTCL subtype has specific symptoms, some common symptoms include:

* Swollen lymph nodes: You may have painless swelling in your neck, armpits or groin.
* Unexplained weight loss: This is losing body weight without trying. Losing 10% of your total body weight over six months is a sign of unexplained weight loss.
* Belly (abdominal) pain or swelling: This may happen if your spleen becomes enlarged.
* Persistent fatigue: This is feeling much more tired than usual for at least several days and for no apparent reason.
* Unexplained fever: Often, fevers are signs your body is fighting an infection. A fever that stays above 103 degrees Fahrenheit (39.5 degrees Celsius) for two or more hours after home treatment or lasts longer than two days may be a sign of a serious problem.

Specific subtypes may have other symptoms.

#### **Peripheral T-cell lymphoma, not otherwise specified**

Symptoms other than ones common to PTCL include:

* Anemia (low red blood cell levels).
* Thrombocytopenia (low platelet levels).
* Itchy red patches on your skin.
* Chest pain or shortness of breath (dyspnea) if there’s cancer in your chest.

#### **Angioimmunoblastic T-cell lymphoma**

Symptoms other than ones common to PTCL include:

* Night sweats.
* Skin rash.
* Autoimmune disorders like autoimmune hemolytic anemia.

#### **Anaplastic large cell lymphoma**

Primary cutaneous ALCL

Symptoms include:

* Abnormal reddish or reddish-brown growths on your skin that grow over time.
* Large, raised bumps that itch.
* Growths that become wounds and scab over.

Systemic ALCL

Systemic ALCL causes common PTCL symptoms.

#### **Extranodal natural killer/T-cell lymphoma, nasal type**

Symptoms include:

* Congestion (your nose feels blocked up).
* Nosebleeds.
* Crust in your nose.
* Painful swelling that affects your face.
* Eye issues like “weepy” eyes or eye pain.

#### **Adult T-cell lymphoma/leukemia**

The four ATLL subtypes have common PTCL symptoms.

### **causes of peripheral T-cell lymphomas**

Peripheral T-cell lymphomas happen when your T cells mutate and become cancerous cells. T cells are white blood cells that help defend your body from intruders like germs. When T cells mutate, they turn into cancerous cells that multiply uncontrollably. As they multiply, they build up in your lymph nodes, spleen, liver and other organs and create cancerous tumors.

Experts don’t know exactly what makes T cells mutate to cause peripheral T-cell lymphoma. But research links them to certain medical conditions. For example, one global study showed having celiac disease may increase your risk of developing several types of PTCL, including anaplastic large cell lymphoma. For another example, being infected with Epstein-Barr virus may increase your risk of developing extranodal natural killer/T-cell lymphoma. Having the human T-cell lymphotropic virus Type 1 (HTLV-1) may increase your risk of acute T-cell lymphoma/leukemia.

## **Diagnosis and Tests**

Healthcare providers may need to do several different tests to find the specific PTCL that’s causing health issues. You may need blood tests, imaging tests, biopsies and genetic tests when pathologists study cancerous cells’ genetic makeup.

#### **Blood tests**

Providers may test your blood for viruses linked to peripheral T-cell lymphomas. Blood tests may include:

* Complete blood count (CBC).
* Comprehensive metabolic panel (CMP).
* Lactate dehydrogenase (LDH) test.
* Hepatitis B and Hepatitis C tests.
* Human immunodeficiency virus (HIV) test.
* Human T-cell lymphotropic virus Type 1 (HTLV-Type 1) tests.

#### **Imaging tests**

Imaging tests give healthcare providers information about what’s going on inside your body, including tumors.

* Computed tomography (CT) scan.
* Positron emission tomography (PET) scan.
* Magnetic resonance imaging (MRI) scan.

#### **Biopsies**

* Lymph node biopsy.
* Skin biopsy.
* Bone marrow biopsy.

### **stages of peripheral T-cell lymphoma**

Providers use cancer staging systems to develop treatment plans and prognoses, or what you may expect from treatment. They set cancer stages based on factors like PTCL type and where the cancerous T cells are growing. Peripheral T-cell lymphoma stages are:

* Stage I: Cancerous T cells in one lymph node or in one cluster of lymph nodes.
* Stage II: Cancer affects two or more clusters of lymph nodes in the same area of your body.
* Stage III: Cancer affects lymph nodes in both the upper and lower parts of your body.
* Stage IV: Cancer affects lymph nodes and other organs like your lungs or your digestive tract.

## **Management and Treatment**

There’s no single treatment for the many PTCL subtypes, and treatment may vary depending on cancer stage. Common treatments may include:

* Chemotherapy, combining different types of chemotherapy drugs.
* Radiation therapy, which providers may use along with chemotherapy.
* Targeted therapy, which targets specific genetic changes or mutations that turn healthy cells into cancerous cells.
* Chemotherapy and allogeneic stem cell transplantation to treat PTCL that doesn’t respond to chemotherapy and radiation therapy or that come back after treatment.

You may want to consider taking part in a clinical trial evaluating PTCL treatments.

#### **common treatment side effects**

Most cancer treatments may cause side effects. For example, chemotherapy and radiation therapy side effects may include:

* Fatigue.
* Chemotherapy brain fog.
* Nausea and vomiting.

## **Outlook / Prognosis**

That depends on the type and stage of PTCL and whether treatment has put cancer into remission. Remission means you don’t have symptoms and tests don’t find signs of cancer. In some situations, standard treatment can cure PTCL. However, most peripheral T-cell lymphomas come back, which means you’ll need additional treatment or a different kind of treatment.

It’s understandable that you want to know what you may expect from treatment. Consider your healthcare provider your best resource for information about your situation.

## **Prevention**

No, they can’t. These lymphomas happen when T cells mutate and become cancerous cells. There’s nothing you can do to prevent that.

## **Living With**

Peripheral T-cell lymphomas are rare, fast-growing cancers. If you have a form of PTCL, here are some suggestions that may help you live with the condition:

* Consider palliative care: This care can help you manage symptoms and treatment side effects. More than that, your palliative care team can support you as you deal with the emotional challenge of living with a serious illness.
* Find support: PTCLs are rare cancers. You may feel as if you’re the only person who knows what you’re going through. You don’t have to face cancer alone. Talk to your healthcare team about support groups so you can connect with others in your situation.
* Take time for self-care: Cancer is stressful. Self-care is an important part of living with PTCL. Talk to your healthcare team about ways to manage stress and how to develop a nutritious diet to keep you strong through treatment.

**EPIDEMIOLOGY**

Experts have found that the overall incidence and frequency of these subtypes varies geographically. PTCL, in general, is more common in Asia and the Caribbean. The most common subtype is called PTCL-not-otherwise specified (PTCL-NOS) and is most frequently diagnosed in individuals living in North America and Europe. Anaplastic large cell lymphoma (ALCL) is common in North America and Europe, whereas angioimmunoblastic T-cell lymphoma (AITL), the second most common subtype, is found more often in Europe. The types known as NK-/ T-cell lymphoma (NKTCL) and adult T-cell leukemia (ATLL) are most common in Asia.

Most PTCL subtypes are aggressive (fast-growing) lymphomas, including PTCL-NOS, AITL, ALCL, enteropathy-type T-cell lymphoma, and extranodal natural killer (NK) cell/T-cell lymphoma.

TCL was thought to occur more frequently in Asia. Rüdiger et al. reported frequencies of PTCL in Vancouver to be 1.6% of all NHL compared to 18.3% in Hong Kong . The international PTCL and NKL project reported PTCL and NKL rates of 5–10% in Western countries compared to 10–20% in Asian countries

In the study, it was also interesting that the incidence of ALCL (both ALK+ and ALK−) in North America (24%) was almost four-times higher than in Asia (6%). Data from Au et al. and our own institution's suggest that the rate of PTCL in the East may actually be similar to the West. The perceived higher rates of PTCL in the East could perhaps be due to the higher incidence of NKL in the East and the differences in diagnostic evaluation. In their institution, they evaluated 148 consecutive cases of TCL and NKL and found that these accounted for 10.1% and 6.5% of all NHL, respectively. We evaluated a total of 780 patients with malignant lymphomas from 2002 to 2006 and found that extranodal NKL and PTCL comprised 5.0% (39/780) and 7.4% (58/780) of all cases

**DIFFERENTIAL DIAGNOSIS**

**Angioimmunoblastic T Cell Lymphoma**

Given the presentation of type B symptoms, rash, lymphadenopathy, differential diagnoses include cutaneous lymphoid neoplasms (including cutaneous lymphomas), infections, an autoimmune disease. The pathological examination of suspicious lesions clinches the diagnosis.

**Large Cell Cutaneous Ki-1 Anaplastic Lymphoma**

Differential diagnosis includes Hodgkin's lymphoma and T-cell lymphomas, in which CD30 can be expressed.

**Cutaneous T-cell Lymphoma**

Benign dermatoses seem to be the most prominent differential diagnoses for cutaneous T-cell lymphomas. These conditions include psoriasis, contact dermatitis, drug eruption. Several of these benign dermatoses may even have T-cell rearrangements (TCR).

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# **High-Grade B-Cell Lymphoma(Double Hit lymphoma)**

**Definition and description**

High-grade B-cell lymphoma (HGBCL, previously known as double-hit lymphoma) is an aggressive type of B-cell non-Hodgkin lymphoma (NHL) characterized by rearrangements (parts of genes switch places within chromosomes) in two particular genes. One rearrangement involves the MYC gene, and the other involves the BCL2 gene or, less commonly, the BCL6 gene.

With respect to gene mutations, HGBCL shares many features with two other types of B-cell lymphomas—diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma. In fact, about five percent of DLBCLs and about 32 to 78 percent of Burkitt lymphomas have rearrangements of the MYC and BCL2/BCL6 genes and are thus called HGBCL. However, research has shown that HGBCL differs in several important ways from the forms of DLBCL and Burkitt lymphoma that do not have dual gene rearrangements. For this reason, in 2016 the World Health Organization designated HGBCL as its own category of B-cell NHL.

Molecular tests allow doctors to check for gene rearrangements in chromosomes under a microscope that are used to confirm a diagnosis of HGBCL.

### **B-cell lymphoma**

B-cell lymphoma is a type of blood cancer in your lymphatic system. In B-cell lymphoma, abnormal lymphocytes (a type of white blood cell) multiply to form tumors. Your lymphatic system is a large network of organs, vessels and tissues, so B-cell lymphoma can develop in many places in your body and cause different symptoms.

B-cell lymphoma is a common type of non-Hodgkin lymphoma. There are many B-cell lymphoma types, but most cause the same symptoms: swollen lymph nodes, fatigue and drenching night sweats.

Often, treatment cures some types of B-cell lymphoma. And there are treatments that put the conditions into remission so you don’t have symptoms and tests don’t find signs of cancer. But the conditions can come back (recur).

#### **Types of B-cell lymphoma**

When your provider talks about your condition, they may use terms like “aggressive” or “indolent” to describe it:

* An aggressive type of B-cell lymphoma is one that can quickly spread (metastasize) from your lymphatic system to other organs or tissues in your body.
* An indolent type of the condition grows more slowly.

##### **Aggressive (fast-growing) B-cell lymphoma**

Aggressive B-cell lymphomas can develop in several areas of your body. Examples include:

* Burkitt lymphoma: This rare, fast-growing lymphoma may develop in your stomach and then spread to other organs.
* Diffuse large B-cell lymphoma (DLBCL): There are different forms of diffuse large B-cell lymphoma. It’s the most common type of non-Hodgkin lymphoma. DLBCL may start in your lymph nodes or a lymphoid organ like your thymus, spleen or tonsils.
* High-grade B-cell lymphoma (HGBCL): This type of B-cell lymphoma causes the same symptoms as DLBCL and Burkitt lymphoma. There are treatments that put the condition into remission, but it often comes back.

##### **Indolent (slow-growing) B-cell lymphoma**

You can have a type of indolent B-cell lymphoma for months and years before you develop symptoms. Common types include:

* Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL): This type develops in your blood and bone marrow.
* Cutaneous B-cell lymphoma: This rare type starts in your skin.
* Follicular lymphoma: This is the second most common type of B-cell lymphoma. You may develop follicular lymphoma in your lymph nodes, bone marrow and other organs.
* Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia): This is a rare type of lymphoma that typically grows in your bone marrow, but may also develop in parts of your lymphatic system.
* Marginal zone lymphomas: There are different types of marginal zone lymphomas. Some develop in your stomach, lungs, skin, thyroid, salivary glands and tissues around your eyes.
* Mantle cell lymphoma: This B-cell lymphoma type often develops in your lymph nodes, bone marrow and spleen.

## **Symptoms and Causes**

You can have a type of B-cell lymphoma without having symptoms. For example, people with follicular lymphoma often receive a diagnosis while receiving treatment or tests for an unrelated condition. Symptoms that may be related to B-cell lymphoma include:

* Abdominal (belly) pain: Some types start in your belly, causing pain that doesn’t go away or gets worse.
* Drenching night sweats: This is sweating so much that your pajamas, sheets and blankets are soaking wet.
* Swollen lymph nodes: Painless lumps in your neck, armpit or groin are very common symptoms.
* Enlarged spleen or liver: B-cell lymphoma in your spleen or liver can make them get larger.
* Loss of appetite: Cancer in your spleen may make it press on your stomach, so you feel full even when you don’t eat very much.
* Persistent fatigue: Abnormal B cells in your bone marrow can affect red blood cell production and cause anemia (low red blood cell levels). Anemia can make you feel exhausted no matter how much rest you get.
* Pruritus (itchy skin): B-cell lymphoma in your liver may cause liver damage symptoms, including itchy skin.
* Rashes or skin lumps: Cutaneous B-cell lymphoma causes rashes, lumps and bumps on your skin. MALT lymphoma, a rare type of B-cell lymphoma, can cause skin changes, including lumps.
* Unexplained fever: A fever that stays above 100.4 degrees Fahrenheit (38.0 degrees Celsius) lasting more than two days or that comes back may be a B-cell lymphoma symptom.
* Unexplained weight loss: This is losing weight without trying to change what you eat and exercising.

B-cell lymphoma may cause symptoms that look and feel a lot like less serious medical issues. For example, swollen lymph nodes are a common B-cell lymphoma symptom. But they’re also a common symptom of colds and flu.

Having one or more of these symptoms doesn’t mean you have a type of B-cell lymphoma. But you should talk to a healthcare provider if you have symptoms that don’t go away or get worse.

### **causes of B-cell lymphoma**

Your B cells protect your body from invaders like bacteria, viruses and cancerous cells. Normally, your body produces new B cells as needed and the cells die once they’ve done their job.

In B-cell lymphoma, normal B cells change (mutate), turning into abnormal cells that multiply uncontrollably, don’t die and can spread from where they started to other areas of your body.

The condition typically happens because there are accidental (sporadic) changes in your B cells as they replicate themselves. Research suggests that sometimes, there’s a connection between B-cell lymphomas and the following issues:

* Autoimmune diseases, like rheumatoid arthritis, inflammatory bowel disease, Sjörgren’s syndrome and other related conditions.
* Being exposed to certain viruses, including HIV (human immunodeficiency virus), Epstein-Barr (mononucleosis) and Kaposi sarcoma human immunodeficiency virus.
* Having a family history of Hodgkin lymphoma.
* Having obesity.

## **Diagnosis and Tests**

A healthcare provider will ask about your symptoms and your medical history. They’ll do a physical examination that may focus on your lymph nodes, liver and spleen. They may refer you to a hematologist-oncologist, a provider who specializes in diagnosing and treating blood cancer. Your specialist may order blood tests, imaging tests and biopsies to diagnose your condition.

#### **Blood tests**

Blood tests for cancer give your healthcare provider a view of your overall health. Specific tests may include:

* Complete blood count (CBC) with differential: This test measures and counts your blood cells and platelets, including your B cells.
* Comprehensive metabolic panel (CMP): Your provider may order this test to check on substances in your blood that may be signs of B-cell lymphoma.
* Lactate dehydrogenase (LDH) levels: This test measures LDH levels. High LDH levels may be a sign of lymphoma or other diseases.

#### **Imaging tests**

Your provider may order the following imaging tests to look for signs of lymphoma in your lymph nodes, liver or spleen:

* CT scans.
* PET scans.
* Ultrasound.

#### **Biopsy**

A biopsy to obtain lymph node tissue is the only way your provider can confirm you have B-cell lymphoma. A medical pathologist will examine lymph node tissue samples to identify the lymphoma type. Biopsies may include:

* Excisional or incisional biopsy: In these procedures, a surgeon makes cuts in your body to remove lymph nodes for examination.
* Fine-needle aspiration (FNA): This procedure involves using a fine needle and a syringe to pull out cells for examination.
* Bone marrow biopsy: Providers use a special biopsy needle to remove a small piece of bone marrow for examination. Bone marrow biopsies are common tests to diagnose blood cancers like B-cell lymphoma.

## **Management and Treatment**

There’s no single treatment for B-cell lymphoma. If you have this condition, your treatment will depend on factors like the type, your overall health and if tests detect the condition before it spreads.

Your hematologist oncologist will recommend treatments that do the most to eliminate cancerous tumors while causing the fewest side effects. You may receive one or more of the following treatments:

* Chemotherapy.
* Immunotherapy.
* Radiation therapy.
* Targeted therapy. These include treatments such as monoclonal antibody therapy.
* Watchful waiting/active surveillance. If you have a type of slow-growing B-cell lymphoma and don’t have symptoms, your provider may do watchful waiting or active surveillance. Providers carefully monitor your overall health so they’re ready to start treatment as soon as you have symptoms.

#### **Common treatment side effects**

Each treatment may cause different side effects. And people often react differently to any given treatment. Your healthcare provider will select treatments that do the most to eliminate cancerous cells with the fewest side effects. Although cancer treatments are different, they do have some common side effects. Common side effects may include:

* Diarrhea.
* Fatigue.
* Nausea and vomiting.

Talk to your healthcare provider about each treatment option and potential side effects. Understanding how your treatment might affect you can help you feel more confident about managing side effects.

Regardless of the kind of treatment that you receive, also ask your provider about palliative care. Palliative care is a specialized treatment to help you manage B-cell lymphoma symptoms and treatment side effects.

## **Outlook / Prognosis**

There are many different types of B-cell lymphoma, so what you can expect depends on your situation and factors like the type of lymphoma, how well your body responded to treatment and your overall health. Your provider is your best resource for information on what to expect.

#### **B-cell lymphoma survival rates**

Survival rates vary widely depending on the type of lymphoma. For example, 64.6% of people with diffuse large B-cell lymphoma are alive five years after diagnosis. On the other hand, data show 90% of people with follicular lymphoma are alive five years after diagnosis.

If you’re receiving treatment for a type of B-cell lymphoma, ask your provider to explain survival rate information for your situation, including whether a survival rate can predict how long you’ll live. And try to keep in mind that any survival rate is an estimate based on the experiences of other people. What was true for them may not be true for you.

## **Living With**

B-cell lymphoma can be a life-changing diagnosis. You may feel overwhelmed as you try to take in information about your condition and treatment while trying to keep up with your daily life. Here are some suggestions that may help you:

* Have a plan for living with B-cell lymphoma. That plan might be lining up support during treatment, whether that’s arranging for special meals, transportation to appointments or someone to keep you company during treatment.
* Eat well. Treatment may affect your appetite. Consider working with a nutritionist so you fill your plate with food that you enjoy.
* Get your rest. Treatment can be exhausting. Plan to rest as much as possible, meaning rest when you need to, not just when you think you have time.
* Consider mental health support. Having cancer may make you feel anxious, angry, overwhelmed or depressed. Working with a mental health provider may help you understand and manage all those emotions.
* Find ways to relieve stress. Cancer is stressful. Consider activities such as meditation, relaxation exercises or deep breathing exercises.
* Reach out for support. Your healthcare provider can direct you to support groups and programs where you can express your feelings and concerns with people who understand what you’re going through.

### **When should I see a doctor**

You’ll see your hematologist-oncologist and other care team members throughout your treatment. They’ll manage your treatment and monitor your overall health. When you finish treatment, your provider may recommend a schedule of regular follow-up appointments so they can watch for signs that B-cell lymphoma is coming back.

## Epidemiology

### Occurrence in the United States

After a striking increase in incidence rates between 1970 and 1995 (which may in part have reflected improved diagnosis), the rates of new non-Hodgkin lymphoma (NHL) cases stabilized. From 2010-2019, rates of new cases fell on average 1.0% each year; and from 2011-2020, death rates fell on average 2.2% each year. The current US age-adjusted rate is 18.6 cases per 100,000 person-years for both sexes.The estimated rate for diffuse large B-cell lymphomas is approximately 4.68 cases per 100,000 person-years.

It is estimated that approximately 80,350 new cases of NHL will be diagnosed and 19,390 patients will die from NHL in 2025, despite currently available treatment.Lymphomas are a heterogeneous group of malignancies with diverse biology, clinical behavior, and prognosis.

In general, lymphomas can be divided into two groups, Hodgkin lymphoma (HL) and NHL. While infrequent, HL (8720 estimated new cases in 2025) is commonly diagnosed in younger patients and is curable with appropriate therapy in 85% of cases. In contrast, NHL is the seventh most common cancer in men and the sixth most common in women in the United States, accounting for 4% of all cancers, and the ninth leading cause of cancer deaths, accounting for 3% of cancer-related deaths.

Diagnosed cases of B-cell non-Hodgkin’s lymphoma (NHL) are set to increase by 15% in the next decade, according to a new analysis.

Analysts GlobalData say the complexity of the disease means health services need a “nuanced” understanding of its subtypes.

They studied the prevalence of the disease in seven wealthy countries: the USA, UK, Japan, France, Germany, Italy and Spain. The researchers say the number of annual diagnoses in these seven countries will increase from 200,844 in 2023 to 229,804 in 2033.

The number of patients living with the disease five years or more will increase from 634,000 to 714,000.

Senior epidemiologist Zachary Natale said: “Despite the progress that has been made, B-cell NHL remains a complex spectrum of malignant neoplasms, each of which exhibits idiosyncratic clinical manifestations and behaviours.

“Due to its heterogeneous impact on the clinical course of patients, it is imperative for healthcare workers, public health professionals, and researchers to develop a more nuanced understanding of B-cell NHL’s subtypes to best address them as respective diseases.”

## **Diagnostic Considerations**

Other problems to be considered include the following:

* Pseudolymphoma syndrome
* Carcinoma of unknown primary, especially in patients who present with significant lymphadenopathy in the mediastinum or abdomen.
* Mycobacterial infections, especially in patients with immune compromise; may manifest as fever, weight loss, and lymphadenopathy and, therefore, clinically mimic lymphoma.
* Fungal infections (eg, histoplasmosis, cryptococcosis in the acute phase) can similarly manifest as lymphadenopathy, fever, and (occasionally) weight loss, simulating lymphoma.

## **Differential Diagnoses**

* Hodgkin Lymphoma
* Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
* Metastatic Cancer With Unknown Primary Site

## Other B-Cell Lymphomas

* Follicular Lymphoma (FL):
  + May have overlapping features with DLBCL, especially grade 3 FL which can resemble large B-cell lymphoma.
  + FL typically shows follicular architecture and expresses germinal center markers (CD10, BCL6).
* Burkitt Lymphoma (BL):
  + Characterized by monomorphic medium-sized cells, very high proliferation index (Ki-67 nearly 100%), and MYC rearrangement.
  + BL lacks large cells typical of DLBCL.
* Mantle Cell Lymphoma (MCL):
  + Usually expresses cyclin D1 and SOX11, with t(11;14) translocation.
  + Cells are typically medium-sized and may mimic DLBCL in blastoid variants.
* B-Lymphoblastic Lymphoma (B-LBL):
  + Immature B-cell neoplasm with TdT positivity, usually in children and young adults.
  + Needs to be distinguished from DLBCL due to different treatment.
* High-Grade B-Cell Lymphomas (HGBCL):
  + Includes “double-hit” and “triple-hit” lymphomas with rearrangements of MYC, BCL2, and/or BCL6.
  + Aggressive clinical behavior; immunophenotypic and cytogenetic studies required.
* Primary Mediastinal Large B-Cell Lymphoma (PMBCL):
  + Occurs in young adults, often females, with mediastinal mass.
  + Shares features with classical Hodgkin lymphoma (cHL) but distinct immunophenotype.

Hodgkin Lymphoma (HL)

* Classical Hodgkin lymphoma can mimic DLBCL, especially PMBCL and gray zone lymphomas.
* Reed-Sternberg cells in HL are CD30+, CD15+, and usually CD20-negative, contrasting with DLBCL which is CD20+.

Benign and Infectious Conditions

* Infectious Mononucleosis (EBV infection):
  + Can cause reactive lymphadenopathy with atypical lymphocytes mimicking lymphoma.
  + Clinical context and serology help differentiate.
* Benign Inoculation Lymphoreticulosis (Cat Scratch Disease):
  + Caused by *Bartonella henselae*, presents with localized lymphadenopathy.
* Metastatic Carcinoma:
  + Metastatic tumors to lymph nodes may mimic lymphoma clinically and radiologically.

Other Hematologic Malignancies

* T-Cell Lymphomas:
  + Some T-cell lymphomas may mimic B-cell lymphomas morphologically but differ immunophenotypically (CD3+, CD20−).

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**GRAY ZONE LYMPHOMA**

Gray zone lymphoma is a rare type of lymphoma that shares characteristics of both Hodgkin’s lymphoma and a type of non-Hodgkin’s lymphoma called primary mediastinal B-cell lymphoma (PMBCL).

Some people are treated for Hodgkin’s lymphoma and PMBCL unsuccessfully before they’re diagnosed with gray zone lymphoma. This confusion is what earned gray zone lymphoma its name when it was first recognized as a distinct type of lymphoma in 2008.

In this article, we’ll take a closer look at gray zone lymphoma, including its symptoms, diagnosis, treatment, and outlook.

## **symptoms of gray zone lymphoma**

Gray zone lymphoma causes swelling in your thymus, a small gland under your breastbone, and in the nearby lymph nodes. As the tumor grows and swelling increases, many people with gray zone lymphoma notice a lump in their chest, near their breast bone.

Sometimes, this swelling is painful or results in pressure in the chest. The tumor growth can also press on the lungs and throat, leading to difficulty eating, talking, and breathing.

Gray zone lymphoma also causes generalized lymphoma symptoms. These include:

* swollen lymph nodes in the neck, groin, or under the arms
* loss of appetite
* unintentional weight loss
* itchy skin
* easy bruising
* excessive bleeding from minor cuts, nosebleeds, or other small injuries
* bleeding gums
* heavy menstrual periods
* fatigue
* night sweats
* high fever

## **Causes of gray zone lymphoma and who’s at risk for it**

Gray zone lymphoma is rare, and there’s no known cause for this cancer. Experts believe that infection with the Epstein-Barr virus can increase the risk of gray zone lymphoma. However, the virus doesn’t directly cause cancer, and people who’ve never had Epstein-Barr can develop gray zone lymphoma.

Research also shows that, while gray zone lymphoma can occur in people of any age or gender, it’s more common in people who are between 20 and 40 years old and in people assigned male at birth.

You’re also more at risk for gray zone lymphoma if you have any risk factors for all types of lymphoma:

* having a family member with lymphoma
* having a family member with chronic leukemia
* having a condition that weakens your immune system
* having an autoimmune condition
* taking a medication that weakens your immune system
* having prolonged workplace exposure to pesticides, herbicides, fungicides, solvents, paints, oil, fuel, infectious organisms, dust, or hair dye.
* having any type of cancer in the past

## **Diagnosis of gray zone lymphoma**

The first step to getting diagnosed with gray zone lymphoma is a medical appointment. At your appointment, your doctor will ask you about your symptoms and your medical history. If they suspect you might have any type of lymphoma, they’ll order tests to help confirm the diagnosis.

Common tests for gray zone lymphoma include:

* Blood tests: Blood tests will look at the numbers of red blood cells, white blood cells, and platelets in your blood. Lymphoma can affect how many of these cells are circulating in your blood.
* Biopsies: Biopsies will be done on any swollen lymph nodes or glands. Biopsies remove samples of the affected node or gland so that it can be tested for cancer in a lab. Typically, biopsies for gray zone lymphoma are done by inserting a thin and hollow needle into the node or gland.

Biopsies are typically the best way to confirm cancer. Once you’ve been diagnosed with gray zone lymphoma, you’ll have additional tests to stage your cancer.

Staging is a system that addresses how far cancer has progressed. It helps doctors plan your treatment and helps you get a better understanding of your outlook. Gray zone lymphoma staging is based on:

* how many areas of your body have lymphoma
* which parts of your body have lymphoma
* whether the lymphoma has spread to your bone marrow
* whether the lymphoma has spread to organs, including the liver, skin, and lungs

### **Staging of gray zone lymphoma**

There are four stages of gray zone lymphoma. In stages 1 and 2, the cancer is in its early stage and hasn’t yet spread throughout the body. In stages 3 and 4, cancer is advanced and has spread throughout the body, including to organs and bone marrow. The exact breakdown of stages is:

* Stage 1: Cancer is contained to one lymph node.
* Stage 2: Cancer is contained to two or more lymph nodes on the same side of the diaphragm
* Stage 3: Cancer is in at least one lymph node above the diaphragm and one lymph node below the diaphragm.
* Stage 4: Cancer has spread throughout the body and to distant organs.

## **Treatment**

Gray zone lymphoma is rare, and there’s no standard treatment. Your doctor will look at your test results and develop the treatment plan that is best for you.

Common gray zone lymphoma treatments include:

* chemotherapy
* radiation therapy
* stem cell transplants

## **What’s the outlook for someone who has gray zone lymphoma?**

Gray zone lymphoma is a rare and unique type of lymphoma that has only recently been recognized. This makes it difficult to obtain the kind of survival statistics that have been gathered for other cancers and conditions.

A 2020 study looked at accumulated data on patients with gray zone lymphoma across the United States. They found that people with gray zone lymphoma had a 68% chance of survival in the 3 years following their diagnosis.

The study also found that age at diagnosis and stage of cancer at diagnosis had a large impact on survival. Younger people who were treated in earlier stages saw much better outcomes.

Epidemiology

Reported as early as 1998, then with more frequency in 2005, GZL was subsequently recognized by the World Health Organization (WHO) in 2008. Due to its rarity, the incidence cannot be estimated definitively, however Qasrawi et al. estimated an incidence rate of 0.53 per million person-years based on confirmed GZL between 2005 and 2016 with age-adjusted incidence rates according to the US Standard Population in the year 2000 [17]. Furthermore, GZL is both a diagnostic and clinical dilemma faced by pathologists for its morphologic and phenotypic complexities and by oncologists for its aggressive clinical course and poor guideline defined treatment options [13,18]. One study recognized 68 cases of GZL across 15 North American Academic Centers and after central pathologic review by 5 hematopathologists, it was determined that only 26 cases were confirmed GZL [19].

Additionally in 2008, GZL had further been characterized as Mediastinal Gray Zone Lymphoma (MGZL) as well as Non-Mediastinal Gray Zone Lymphoma (NMGZL). MGZL is the name applied to gray zone lymphoma that has similar morphologic and phenotypic features to both classic Hodgkin's lymphoma and PMBL, and is found in the mediastinum. Typically, it affects young men and children with a male to female predominance of 1.4:1, which is notably different than PMBL and classic Hodgkin's lymphoma which have a female predominance. The mean age is 32–37 years which is also similar to the age of incidence in both CHL and PMBL [20,21].

NMGZL, which was previously thought to represent a heterogeneous subset of GZL, is no longer classified as a subset of GZL as of 2022. Cases with morphologic and immunophenotypic features similar to MGZL, but presenting outside and without involvement of the mediastinum should be classified as Diffuse Large B-cell Lymphoma not otherwise specified (DLBCL, NOS)

## Main Differential Diagnoses

| **Diagnosis** | **Key Distinguishing Features** |
| --- | --- |
| Classical Hodgkin Lymphoma (cHL) | Presence of Reed-Sternberg cells; strong CD30 and CD15 expression; weak or absent B-cell markers (CD20 usually negative or weak); OCT-2 and BOB.1 negative or weak; usually CD45 negative. |
| Primary Mediastinal Large B-Cell Lymphoma (PMBCL) | Strong expression of B-cell markers (CD20, CD79a, PAX5), OCT-2 and BOB.1 positive; CD30 positive but weaker and more heterogeneous than cHL; absence of CD15; typically lacks Reed-Sternberg cells. |
| Diffuse Large B-Cell Lymphoma (DLBCL), Not Otherwise Specified | Lacks the characteristic mediastinal presentation and overlapping immunophenotype; usually strong B-cell marker expression and absence of cHL features. |
| EBV-Positive Lymphomas | EBV+ cHL and EBV+ DLBCL need to be considered, especially in EBV+ GZL cases. EBV status assessed by EBER in situ hybridization. |
| Other Mediastinal Masses | Thymoma, germ cell tumors, other lymphomas (e.g., nodular lymphocyte-predominant Hodgkin lymphoma) may be considered clinically but distinguished histologically. |

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### **Multiple Myeloma**

**Definition and description**

Multiple myeloma is a cancer that forms in a type of white blood cell called a plasma cell. Healthy plasma cells help fight infections by making proteins called antibodies. Antibodies find and attack germs.

* In multiple myeloma, cancerous plasma cells build up in bone marrow. The bone marrow is the soft matter inside bones where blood cells are made. In the bone marrow, the cancer cells crowd out healthy blood cells. Rather than make helpful antibodies, the cancer cells make proteins that don't work right. This leads to complications of multiple myeloma.
* Multiple myeloma treatment isn't always needed right away. If the multiple myeloma is slow growing and isn't causing symptoms, close watching might be the first step. For people with multiple myeloma who need treatment, there are a number of ways to help control the disease.

## **How does multiple myeloma start?**

When plasma cells become cancerous and grow out of control, this is generally called multiple myeloma.

Plasma cells are a type of white blood cell found in your bone marrow. They are one of several types of cells in your immune system that work together to fight infections and other diseases.

Normal plasma cells fight off infections by making proteins called antibodies (also called immunoglobulins) which help your body attack and kill germs. But sometimes, plasma cells become cancerous and grow out of control.

When this happens, the plasma cells make an abnormal antibody. This antibody is known by different names, including monoclonal immunoglobulin, monoclonal protein (M-protein), M-spike, or paraprotein.

### **Plasma cell disorders**

Plasma cells sometimes grow in other, unusual ways that don’t meet the criteria to be called active multiple myeloma. These conditions are described in Other Plasma Cell Disorders (below).

## **Multiple myeloma features**

Multiple myeloma can affect the blood, bones, and other organs, which can lead to problems in different parts of the body.

### **Low blood counts**

In multiple myeloma, the overgrowth of plasma cells in the bone marrow can crowd out normal blood-forming cells, leading to low blood counts.

* Anemia (a shortage of red blood cells) can cause a person to feel weak, fatigued (tired), or short of breath.
* Thrombocytopenia (a shortage of platelets in the blood) can lead to an increased risk of bleeding and bruising.
* Leukopenia (a shortage of normal white blood cells) can increase the risk of infections.

### **Bone and calcium problems**

Myeloma cells can also interfere with cells that help keep bones strong. Two kinds of bone cells constantly work together to keep bones healthy and strong:

* Osteoclasts break down old bones.
* Osteoblasts lay down new bones.

Myeloma cells make a substance that tells the osteoclasts to speed up dissolving the bone. So old bone is broken down without new bone to replace it, making the bones weak and easy to break. Fractured bones are a major problem in people with myeloma.

### **Infections**

Abnormal plasma cells can’t protect your body from infections. Normal plasma cells make antibodies that attack germs. But in multiple myeloma, the myeloma cells crowd out the normal plasma cells, so antibodies that fight infections can’t be made.

### **Kidney problems**

The antibodies made by myeloma cells can harm your kidneys, leading to kidney damage or even kidney failure.

## **Other plasma cell disorders**

A few plasma cell disorders involve unusual plasma cell growth but don’t meet the criteria for active multiple myeloma. These include:

* Monoclonal gammopathy of undetermined significance (MGUS)
* Solitary plasmacytoma
* Smoldering multiple myeloma (SMM)
* Light chain amyloidosis

### **Monoclonal gammopathy of undetermined significance (MGUS)**

In monoclonal gammopathy of undetermined significance (MGUS), abnormal plasma cells make many copies of the same antibody (called a monoclonal protein). However, these plasma cells don’t form an actual tumor or mass, and they don’t cause the other health problems that can be seen in multiple myeloma.

MGUS doesn’t damage bones or cause high calcium levels, kidney problems, or low blood counts. It’s most often found when a routine blood test finds a high level of protein in the blood and further testing shows the protein is a monoclonal antibody.

In MGUS, the number of plasma cells may be increased, but they still make up less than 10% of the cells in the bone marrow.

MGUS is not considered cancer, but some people with MGUS will eventually develop a cancer such as multiple myeloma or lymphoma. They might also develop amyloidosis, a condition linked with blood cancers (see below). Each year, about 1% of people with MGUS develop one of these diseases. The risk is greater in people whose monoclonal protein levels are particularly high.

People with MGUS don’t need treatment, but they are watched closely to see if they get a disease that *does* need to be treated, such as multiple myeloma.

**Causes of MGUS**

Experts don't know what causes MGUS. Changes in genes and being around certain chemicals, such as those used to kill pests, appear to play a role.

**Risk factors of MGUS**

Factors that increase your risk of developing MGUS include:

* **Age.** The average age at diagnosis is 70 years.
* **Race.** Africans and Black Americans are more likely to get MGUS than white people are.
* **Sex.** MGUS is more common in men.
* **Family history.** Having family members with MGUS might increase the risk.

**Complications of MGUS**

Each year, about 1% of people with MGUS get certain types of blood cancers or other serious diseases, such as:

* Multiple myeloma.
* Light chain amyloidosis.
* Waldenstrom macroglobulinemia.
* Lymphoma.

Other issues linked to MGUS include broken bones, blood clots, kidney problems, and damage to nerves outside of the brain and spinal cord, also known as peripheral neuropathy.

## **Diagnosis of MGUS**

Because MGUS usually causes no symptoms, people who have it usually find out by chance during blood tests for other reasons. After that, other tests might include:

* **More blood tests.** These can help rule out other causes of higher protein levels. And they can check for kidney damage.
* **Urine tests.** Urine samples taken over 24 hours can help find if the atypical protein is in the urine. They also can check for kidney damage.
* **Imaging tests.** For people with bone pain, an MRI or positron emission tomography (PET) scan can look for problems with bones from MGUS. They also might need a test to measure bone mass, also known as bone density.
* **Bone marrow test.** A hollow needle removes a piece of bone marrow from the back of one of the hip bones for study. This usually is only for those at risk of getting a more serious disease or other problems linked to MGUS.

**Treatment of MGUS**

MGUS doesn't require treatment. But your health care provider is likely to have you get regular checkups to watch the condition. Checkups likely will start six months after your diagnosis.

### **Watchful waiting**

For those at high risk of MGUS leading to a more serious condition, more-frequent checkups can watch the disease. That way, treatment can start as soon as possible if it's needed.

Symptoms to watch for include:

* Bone pain.
* Tiredness or weakness.
* Weight loss without trying.
* Fever or night sweats.
* Headache, dizziness, nerve pain, or changes in vision or hearing.
* Bleeding.
* Anemia or other blood irregularities.
* Swollen lymph nodes, liver or spleen.

### **Medicines**

Medicine for the bone-thinning disease known as osteoporosis increases bone mass. Examples include alendronate (Fosamax), risedronate (Actonel, Atelvia), ibandronate and zoledronic acid (Reclast, Zometa).

### **Solitary plasmacytoma**

A plasmacytoma is a type of plasma cell tumor. Rather than many tumors in different locations as in multiple myeloma, there is only one tumor, hence the name solitary plasmacytoma.

A solitary plasmacytoma often develops in a bone. When a plasmacytoma starts in other body tissues (such as the lungs or other organs), it is called a solitary extramedullary (or extraosseous) plasmacytoma.

Solitary plasmacytomas can usually be treated with radiation therapy and/or surgery. As long as no other plasmacytomas are found later on, the person’s outlook is usually excellent. However, people with a solitary plasmacytoma might develop multiple myeloma later, so they need to be watched closely for signs of this disease.

### **Smoldering multiple myeloma ﻿(SMM)**

Smoldering multiple myeloma (SMM), also known as asymptomatic myeloma, is an early form of myeloma that is not causing any symptoms. People with smoldering myeloma have some signs of multiple myeloma, such as any of the following:

* A higher-than-normal amount of plasma cells in the bone marrow
* A high level of monoclonal immunoglobulin (monoclonal protein) in the blood
* A high level of light chains (also called Bence Jones protein) in the urine

However, they have normal blood counts, normal calcium levels, normal kidney function, no bone or organ damage, and no signs of amyloidosis (see below).

Most people with smoldering multiple myeloma don’t need treatment right away, because the disease can take anywhere from many months to years to become active (symptomatic) myeloma.

Some people may have very slow disease that never becomes active myeloma, but for others the risk is higher, so earlier treatment might be helpful.

### **Light chain amyloidosis**

Light chain amyloidosis (also known as AL amyloidosis or primary amyloidosis) is also a disorder of abnormal plasma cell growth, but with lower amounts of abnormal plasma cells in the bone marrow compared to multiple myeloma.

Monoclonal proteins (antibodies) are made up of joined protein chains – 2 short light chains and 2 longer, heavy chains. In light chain amyloidosis, abnormal plasma cells make too many light chains. The light chains build up in tissues as an abnormal protein known as amyloid.

The buildup of amyloid in certain organs can enlarge them and affect the way they work. For example:

* When amyloid builds up in the heart, it can cause an irregular heartbeat and can make the heart larger and weaker. A weak heart can lead to a condition called congestive heart failure, with symptoms like shortness of breath and swelling in the legs.
* Amyloid in the kidneys can affect how well they work. This may not cause symptoms early on, but the poor kidney function may be seen on blood tests. If it gets bad enough, it can lead to kidney failure.

Light chain amyloidosis is only one of the diseases where amyloid builds up and causes problems. Amyloidosis can also be caused by a genetic (hereditary) disease called familial amyloidosis. Long-standing (chronic) infection and/or inflammation can also cause amyloidosis. This is known as secondary or AA amyloidosis.

### **Waldenstrom macroglobulinemia (WM)**

The cancer cells in people with WM are similar to those in multiple myeloma and non-Hodgkin lymphoma (NHL). Multiple myeloma is considered a cancer of plasma cells, and non-Hodgkin lymphoma is a cancer of lymphocytes. WM cells have features of both plasma cells and lymphocytes*.*

Lymphocytes are one of the main types of white blood cells in the immune system. They include T cells and B cells, and they are in many areas of your body, including your lymph nodes, bone marrow, intestines, and bloodstream. When B cells respond to an infection, they mature and change into plasma cells.

Even though WM is sometimes grouped with other plasma cell disorders, it is considered a type of NHL.

Waldenstrom macroglobulinemia grows slowly. It might not cause symptoms for years.

When they happen, Waldenstrom macroglobulinemia symptoms may include:

* Fatigue.
* Fever.
* Weight loss.
* Night sweats.
* Numbness in the hands or feet.
* Swollen lymph nodes.
* A feeling of pain or fullness under the ribs on your left side, which may be caused by an enlarged spleen.
* Easy bruising.
* Bleeding nose or gums.
* Headache.
* Shortness of breath.
* Changes in vision.
* Confusion.

**Causes of waldenstrom macroglobulinemia**

Cancer happens when cells develop changes in their DNA. A cell's DNA holds the instructions that tell a cell what to do. The changes tell the cells to multiply quickly. The cells continue living when healthy cells would die as part of their natural lifecycle.

In Waldenstrom macroglobulinemia, the changes happen in the white blood cells. The changes turn some of the white blood cells into cancer cells. It's not clear what causes the changes.

The cancer cells can build up in the spongy material inside the bones where blood cells are made. This material is called bone marrow. The cancer cells crowd healthy blood cells out of the bone marrow. The cancer cells also may build up in the lymph nodes and the spleen.

Waldenstrom macroglobulinemia cells make a protein that the body can't use. The protein is immunoglobulin M, which is also called IgM. IgM can build up in the blood. This may reduce blood flow in the body and cause other problems.

**Risk factors OF WALDENSTROM MACROGLOBULINEMIA**

Factors that can increase the risk of Waldenstrom macroglobulinemia include:

* **Being older.** Waldenstrom macroglobulinemia can occur at any age, but it's most often found in adults 70 and older.
* **Being male.** Males are more likely to have Waldenstrom macroglobulinemia.
* **Being white.** White people are more likely to develop the disease, compared with people of other races.
* **Having a family history of lymphoma.** Having a relative who has Waldenstrom macroglobulinemia or another type of B-cell lymphoma might increase your risk.

## **Diagnosis and test of waldenstrom macroglobulinemia**

A physical exam, medical history and the following tests are used to diagnose Waldenstrom macroglobulinemia:

* **Blood tests.** Blood tests can show if there are too few healthy blood cells. Also, blood tests detect a protein made by the cancer cells. This protein is immunoglobulin M, which is also called IgM.  
  Blood tests also can show how well organs are working. Results can show whether the IgM proteins are harming organs, such as the kidneys and the liver.
* **Collecting a sample of bone marrow for testing.** During a bone marrow biopsy, a needle is used to take some bone marrow from the hipbone. The sample goes to a lab where it is tested for cancer cells. If there are cancer cells, more tests can give more information about the cells.
* **Imaging tests.** Imaging tests can help show whether cancer has spread to other areas of the body. Imaging tests might include CT scans or positron emission tomography scans, which are also called PET scans.

**Treatment of waldenstrom macroglobulinemia**

Treatment options for Waldenstrom macroglobulinemia may include:

* **Watchful waiting.** If IgM proteins are in the blood, but there are no symptoms, treatment might not be needed right away. Instead, you might have blood tests every few months to monitor your condition. Doctors sometimes call this watchful waiting. There might be no need for treatment for years.
* **Plasma exchange.** Plasma exchange, also known as plasmapheresis, removes IgM proteins from the blood. It replaces them with healthy blood plasma. Plasma exchange can relieve symptoms caused by having too many IgM proteins in the blood.
* **Chemotherapy.** Chemotherapy uses strong medicines to kill cancer cells throughout the body. Chemotherapy used alone or with other medicines might be the first treatment for people who have symptoms of Waldenstrom macroglobulinemia. Also, high-dose chemotherapy can stop bone marrow from making cells and may be used to prepare for a bone marrow transplant.
* **Targeted therapy.** Targeted therapy uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Targeted therapy medicines might be used with other treatments, such as chemotherapy or immunotherapy.
* **Immunotherapy.** Immunotherapy is a treatment with medicine that helps your body's immune system to kill cancer cells. Your immune system fights off diseases by attacking germs and other cells that shouldn't be in your body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.
* **Bone marrow transplant.** In select instances, a bone marrow transplant, also known as a stem cell transplant, may be a treatment for Waldenstrom macroglobulinemia. During this procedure, high doses of chemotherapy wipe out the bone marrow. Healthy blood stem cells go into the body to rebuild healthy bone marrow.
* **Supportive care.** Supportive care, which is also called palliative care, focuses on relieving pain and other symptoms of serious illness. This extra layer of care can support you as you undergo other treatments, such as chemotherapy.

**Causes of myeloma**

It's not clear what causes myeloma.

Multiple myeloma begins with one plasma cell in the bone marrow. The bone marrow is the soft matter inside bones where blood cells are made. Something happens that turns the plasma cell into a cancerous myeloma cell. The myeloma cell begins making a lot more myeloma cells quickly.

Healthy cells grow at a set pace and die at a set time. Cancer cells don't follow these rules. They make a lot of extra cells. The cells continue living when healthy cells die. In myeloma, the cancer cells build up in the bone marrow and crowd out the healthy blood cells. This leads to tiredness and not being able to fight infections.

The myeloma cells continue trying to make antibodies, as healthy plasma cells do. But the body can't use these antibodies, called monoclonal proteins or M proteins. Instead, the M proteins build up in the body and cause problems, such as damage to the kidneys. Myeloma cells can damage bones and increase the risk of broken bones.

### **A connection with MGUS**

Multiple myeloma starts as a condition called monoclonal gammopathy of undetermined significance, also called MGUS. In MGUS, the level of M proteins in the blood is low. The M proteins don't cause damage in the body.

**Symptoms of multiple myeloma**

Early in multiple myeloma, there might be no symptoms. When signs and symptoms happen, they can include:

* Bone pain, especially in the spine, chest or hips.
* Nausea.
* Constipation.
* Loss of appetite.
* Mental fogginess or confusion.
* Tiredness.
* Infections.
* Weight loss.
* Weakness.
* Thirst.
* Needing to urinate often.

### 

### **When to see a doctor**

Make an appointment with a doctor or other health care professional if you have symptoms that worry you.

### **Stages**

The results of your tests help your healthcare team decide your myeloma's stage. In multiple myeloma, the stages range from 1 to 3. The stage tells your health care team how quickly your myeloma is growing. A stage 1 multiple myeloma is growing slowly. As the stages get higher, the myeloma becomes more aggressive. A stage 3 multiple myeloma is getting worse quickly.

Multiple myeloma can also be given a risk level. This is another way to say how aggressive the disease is.

Your health care team uses the multiple myeloma stage and risk level to understand your prognosis and plan your treatment.

## **Drug therapy used to treat multiple myeloma**

A single drug might sometimes be used to treat multiple myeloma. But most often, 2 to 4 different kinds of drugs are combined because this tends to work better. The choice of which drugs to use depends on many factors, including:

* T﻿he traits of the myeloma (including if it's considered high risk or standard risk)
* Your age, kidney function, and overall health
* If you might get a stem cell transplant as part of your treatment﻿

The rest of this page gives information about the medicines used to treat multiple myeloma, including their possible side effects. To learn more about how some of these medicines might be combined,

**Immunomodulatory drugs (IMiDs)**

Immunomodulatory drugs (IMiDs) affect the immune system, although exactly how they do this isn’t entirely clear. These drugs are often helpful in treating multiple myeloma.

IMiDs are taken daily as pills, with breaks from treatment on certain days each month. Because these drugs can increase the risk of serious blood clots, they are often given along with aspirin or a blood thinner.

IMiDs might cause severe birth defects when taken during pregnancy, so you can only get them through a special program run by the drug company that makes them.

### **Thalidomide (Thalomid)**

Thalidomide was the first IMiD used to treat multiple myeloma.

Side effects of thalidomide can include drowsiness, fatigue, severe constipation, and painful nerve damage (neuropathy). The neuropathy can be severe, and it might 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.

### **Lenalidomide (Revlimid)**

Lenalidomide is similar to thalidomide, although it tends to have less severe side effects. This is often the first IMiD used in treating multiple myeloma.

The most common side effects of lenalidomide are low blood platelet counts (thrombocytopenia), low white blood cell counts, and diarrhea. It can also cause painful nerve damage. The risk of blood clots is not as high as with thalidomide, but it is still increased.

### **Pomalidomide (Pomalyst)**

Pomalidomide can also be used to treat multiple myeloma, most often after other treatments have been tried.

Some common side effects of pomalidomide include low red blood cell counts (anemia), low white blood cell counts, and fatigue. The risk of nerve damage is not as high as with the other IMiDs. There is also an increased risk of blood clots.

## **Corticosteroids (steroids)**

Corticosteroids, such as dexamethasone and prednisone, are an important part of the treatment of multiple myeloma. They can be used alone or combined with other drugs as a part of treatment.

Corticosteroids can also be used to help reduce the nausea and vomiting that chemo might cause.

### **Side effects of corticosteroids**

Common side effects of corticosteroids can include:

* High blood sugar
* Increased appetite and weight gain
* Problems sleeping
* Changes in mood, such as becoming irritable or “hyper”

When corticosteroids are used for a long time, they can also suppress your immune system, which increases the risk of serious infections. Steroids can also weaken your bones.

Most of these side effects go away over time after the drug is stopped.

## **Proteasome inhibitors**

Proteasome inhibitors stop enzyme complexes (proteasomes) in your cells from breaking down certain proteins that are important for controlling cell division. These drugs affect tumor cells more than normal cells.

### **Bortezomib (Velcade)**

Bortezomib was the first proteasome inhibitor to be approved, and it’s often used to treat multiple myeloma. It may be especially helpful in treating people with kidney problems.

It’s injected into a vein (IV) or under the skin, once or twice a week.

Common side effects of bortezomib include:

* Nausea and vomiting
* Tiredness
* Diarrhea
* Constipation
* Fever
* Loss of appetite
* Lowered blood counts, especially platelet counts (which can cause easier bruising and bleeding) and white blood cell counts (which can increase the risk of serious infection)

Bortezomib can also cause nerve damage (peripheral neuropathy) that can lead to problems with numbness, tingling, or even pain in the hands and feet. The risk of nerve damage is less when the drug is given weekly under the skin.

Some people get shingles (herpes zoster) while taking this drug. To help prevent this, your doctor may have you take an antiviral medicine (like acyclovir) while you take bortezomib.

### **Carfilzomib (Kyprolis)**

Carfilzomib is a proteasome inhibitor that can be used to treat multiple myeloma. It’s given as an injection into a vein (IV), typically once or twice a week. To help prevent problems like allergic reactions during the infusion, the steroid drug dexamethasone is often given before each dose in the first cycle.

Common side effects of carfilzomib include:

* Tiredness
* Nausea and vomiting
* Diarrhea
* Shortness of breath
* Fever
* Low blood counts, including platelet counts (which can cause easier bruising and bleeding) and red blood cell counts (which can lead to tiredness and shortness of breath)

People on this drug can also have more serious problems, such as pneumonia, heart problems, and kidney or liver failure.

### **Ixazomib (Ninlaro)**

Ixazomib is a proteasome inhibitor that is taken by mouth as a capsule, typically once a week for 3 weeks, followed by a week off. This drug is usually given after other drugs have been tried.

Common side effects of ixazomib include:

* Nausea and vomiting
* Diarrhea
* Constipation
* Swelling in the hands or feet
* Back pain
* Lowered blood platelet counts (which can cause easier bruising and bleeding)

This drug can also cause nerve damage (peripheral neuropathy) that can lead to problems with numbness, tingling, or even pain in the hands and feet.

## **Monoclonal antibodies**

Antibodies are proteins made by the body’s immune system to help fight infections. Man Made versions (monoclonal antibodies) can be designed to attack a specific target, such as proteins on the surface of myeloma cells.

### **Antibodies against CD38**

The CD38 protein is found on myeloma cells. Monoclonal antibodies that target this protein seem to work both by killing the cancer cells directly and by helping the immune system attack them.

#### **Daratumumab (Darzalex and Darzalex Faspro)**

Daratumumab is a monoclonal antibody that attaches to the CD38 protein. This drug is used mainly in combination with other types of drugs, although it can also be used by itself in people who have already had other treatments for myeloma.

This drug can be given as an infusion into a vein (IV). A newer form of the drug, known as daratumumab and hyaluronidase (Darzalex Faspro), can be given as a subcutaneous injection (under the skin). This is typically done in the belly area over a few minutes.

Either form of this drug can cause a reaction in some people, either while it’s being given or within several hours afterward. These reactions can sometimes be severe. Symptoms can include coughing, wheezing, trouble breathing, tightness in the throat, a runny or stuffy nose, feeling dizzy or lightheaded, headache, rash, and nausea.

Other side effects can include fatigue, nausea, back pain, fever, and cough. This drug can also lower blood cell counts, which can increase the risk of infections and bleeding or bruising. Darzalex Faspro can also cause reactions at the injection site, such as swelling, itching, and redness.

#### **Isatuximab (Sarclisa)**

Isatuximab is another monoclonal antibody that attaches to the CD38 protein on myeloma cells.

This drug is used along with other types of myeloma drugs, either after other treatments have been tried or as part of the first treatment for some people. It’s given as an infusion into a vein (IV), typically once every 1, 2, or 4 weeks.

Isatuximab can cause a reaction in some people, while it’s being given or within a few hours afterward. These reactions can sometimes be severe. Symptoms can include coughing, wheezing, trouble breathing, tightness in the throat, chills, feeling dizzy or lightheaded, headache, rash, and nausea.

The most common side effects of isatuximab include respiratory infections (such as colds or pneumonia) and diarrhea. This drug can also lower blood cell counts:

* Having too few white blood cells can increase your risk for infections.
* Having too few red blood cells (anemia) can make you feel tired and weak.
* Having too few blood platelets can increase your risk of bleeding and bruising easily.

This drug might also increase your risk of developing a second cancer.

### **Antibodies against SLAMF7**

SLAMF7 is another protein found on myeloma cells. Antibodies that target this protein can help the immune system attack the cancer cells.

#### **Elotuzumab (Empliciti)**

Elotuzumab is a monoclonal antibody that attaches to the SLAMF7 protein. This drug is used in combination with other medicines, mainly in people who have already had other treatments for their myeloma. It’s given as an infusion into a vein (IV).

This drug can cause a reaction in some people, while it’s being given or within several hours afterward. These reactions can sometimes be severe. Symptoms can include fever, chills, feeling dizzy or lightheaded, rash, wheezing, trouble breathing, tightness in the throat, or a runny or stuffy nose.

Other common side effects of Elotuzumab include fatigue, fever, loss of appetite, diarrhea, constipation, cough, upper respiratory tract infections, pneumonia, and nerve damage resulting in weakness or numbness in the hands and feet (peripheral neuropathy).

## **T-cell engagers (TCEs)**

Some newer man made antibodies are designed to attach to two different targets. These are known as bispecific antibodies.

An example is T-cell engagers (TCEs). Once in the body, one part of these antibodies attaches to the CD3 protein on immune cells called *T cells*. Another part attaches to a specific protein on myeloma cells. This brings the two cells together, which helps the immune system attack the myeloma cells.

These medicines can be an option to treat multiple myeloma, typically after other types of drugs have been tried.

### **Teclistamab (Tecvayli)**

Teclistamab attaches to the BCMA protein on myeloma cells. This drug is given as an injection under the skin (subcutaneously), typically once every few days for the first week, then once a week. After several months, it can also be given once every 2 weeks.

### **Elrenatamab (Eltex Fio)**

Elrenatamab also attaches to the BCMA protein on myeloma cells. This drug is given as an injection under the skin (subcutaneously), typically once every few days for the first week, then once a week for several months, and then once every 2 weeks.

### **Talquetamab (Talvey)**

Talquetamab attaches to the GPRC5D protein on myeloma cells (and some other cells). This drug is given as an injection under the skin (subcutaneously), typically once every few days for the first week, then either once a week or once every other week.

### **Side effects of TCEs**

TCEs can cause serious side effects when you first get them. Because of this, you will be starting on a low dose. You might be given other medicines to help lower your risk of side effects, and you might need to stay in the hospital for a day or two after the first few doses.

Common side effects of TCEs include:

* Fever
* Feeling very tired
* Headache
* Nausea
* Diarrhea
* Muscle and joint pain
* Respiratory infections (including pneumonia)
* Low blood cell counts
* Skin rash
* Liver problems﻿

More serious side effects of TCEs can include:

* Cytokine release syndrome (CRS): A serious side effect in which T cells in the body release chemicals (cytokines) that ramp up the immune system. This happens most often within the first day after treatment, and it can sometimes be life-threatening. Symptoms can include high fever and chills, feeling dizzy or lightheaded, trouble breathing, low blood pressure, headache, and a very fast heartbeat.
* Nervous system problems: These drugs might affect the nervous system, which could lead to symptoms such as headaches, numbness or tingling in your hands or feet, feeling dizzy or confused, having trouble speaking or understanding things, memory loss, abnormal sleep patterns, tremors, or seizures.
* Infections: These drugs can increase the risk of infection, both in the short term and the long term. Your doctor may recommend medicines to help prevent or treat a possible infection before you have any symptoms.

Your health care team will watch you closely for possible signs of these problems, especially during and after the first few treatments. Be sure to contact them right away if you have any of the symptoms above.

These drugs might also cause other problems. Ask your health care team what you should look out for.

## **Traditional chemotherapy**

Chemotherapy (chemo) is the use of certain kinds of drugs that destroy or control the growth of cancer cells. These drugs can be taken by mouth or given in a vein or a muscle. They enter the bloodstream and reach almost all areas of the body.

At one time, chemo was often part of the main treatment for multiple myeloma. As newer types of drugs have become available in recent years, chemo has become less important in treating myeloma, although it still might be used in some situations.

Chemo drugs that can be used to treat multiple myeloma include:

* Cyclophosphamide
* Etoposide (VP-16)
* Doxorubicin (Adriamycin)
* Liposomal doxorubicin
* Melphalan
* Bendamustine
* Cisplatin
* Carmustine

Often, one of these drugs is combined with other types of drugs like corticosteroids and immunomodulating drugs (IMiDs, see above). If a stem cell transplant is planned as part of treatment, most doctors avoid using certain chemo drugs, like melphalan, that can damage bone marrow.

### **Chemo side effects**

Chemo drugs kill cancer cells but also can damage normal cells, which can lead to side effects. These side effects depend on the type and dose of drugs given and how long they are taken. Common side effects of chemo include:

* Hair loss
* Mouth sores
* Loss of appetite
* Nausea and vomiting
* Diarrhea or constipation

Chemotherapy often leads to low blood counts, which can cause:

* An increased risk of serious infection (from having too few white blood cells)
* Easy bruising or bleeding (from having too few blood platelets )
* Feeling tired or short of breath (from having too few red blood cells)

Most side effects go away after treatment is finished.

If you have side effects, your cancer care team can suggest steps to ease them. For example, drugs can be given along with the chemo to prevent or reduce nausea and vomiting.

Along with these short-term side effects, some chemo drugs can cause long-term damage to certain organs such as the heart or kidneys. The possible risks of these drugs are carefully balanced against their benefits, and the function of these organs is carefully monitored during treatment.

## **Nuclear export inhibitor**

The nucleus of a cell holds most of the cell’s genetic material (DNA) needed to make the proteins the cell uses to function and stay alive. A protein called XPO1 helps carry other proteins from the nucleus to other parts of the cell.

### **Selinexor (Xpovio)**

Selinexor is a drug known as a nuclear export inhibitor. It works by blocking the XPO1 protein. When the myeloma cell cannot transport proteins from its nucleus, the cell dies.

This drug is a pill that can be taken weekly or on the first and third day of each week. It can be used, along with the steroid dexamethasone:

* For people whose myeloma is no longer responding to other myeloma drugs, OR
* Along with bortezomib for people whose myeloma has grown on at least one other drug therapy

Common side effects of selinexor include low platelet counts, low white blood cell counts, diarrhea, nausea, vomiting, not feeling hungry, weight loss, low blood sodium levels, and infections like bronchitis or pneumonia.

## **Bisphosphonates and other drugs for bone disease**

Myeloma cells can weaken and even break bones. Drugs that affect bone cells can help bones stay strong by slowing down this process. They can also help reduce pain in the weakened bone(s). Sometimes, pain medicines such as NSAIDs or opioids will be given along with one of these medicines to help control or lessen pain from the bones.

The drugs used most often for treating bone problems in people with myeloma are the bisphosphonates pamidronate (Aredia) and zoledronic acid (Zometa) and the drug denosumab (Xgeva and other brand names).

Treatment with one of these drugs helps prevent further bone damage and events related to weakened bones such as fractures, hypercalcemia (high blood calcium levels), and spinal cord compression in people with multiple myeloma.

### **How bone medicines are given**

These drugs are given intravenously (IV or into a vein) or subcutaneously (under the skin). Most people are treated once a month at first, but they may eventually be treated less often if they are doing well.

Treatment with one of these drugs is often given for up to 2 years, after which the need for continuing it is reassessed. If the myeloma comes back and new bone problems develop, treatment with a bone-disease drug is usually started again.

Talk with your cancer care team to learn more about stopping and restarting treatment with these medicines.

### **Common side effects of bone medicines**

* Side effects of bisphosphonates can include flu-like symptoms and bone or joint pain. These drugs (especially zoledronic acid) can also cause kidney problems, so people with poor kidney function might not be able to take them.
* Common side effects of denosumab can include nausea, diarrhea, and feeling weak or tired. This drug can be given safely to people with kidney problems.

### **Osteonecrosis of the jaw (ONJ)**

All of these bone medicines can have a rare but serious side effect called osteonecrosis of the jaw (ONJ), in which part of the jaw bone loses its blood supply and dies. This can lead to an open sore that doesn’t heal. It can also lead to tooth loss in that area. The jaw bone can also become infected.

Doctors aren’t sure why this happens or how best to prevent it, but having jaw surgery or having a tooth removed can sometimes trigger this problem, so it's important to avoid these procedures while you are taking any of these medicines.

One way to avoid these procedures is to maintain good oral hygiene by flossing, brushing, making sure that dentures fit properly, and having regular dental checkups. Any tooth or gum infections should be treated right away.

Dental fillings, root canal procedures, and tooth crowns do not seem to lead to ONJ. If ONJ does happen, the doctor will stop the bone medicine.

Your doctor might recommend that you have a dental checkup before starting one of these medicines. They might also recommend taking calcium and vitamin D supplements while taking the medicine to help your body build bone.

### **Treating complications**

## Treatment might include treating complications of multiple myeloma. For example:

## Bone pain. Pain medications, radiation therapy and surgery may help control bone pain.

## Kidney damage. People with severe kidney damage may need dialysis.

## Infections. Vaccines can help prevent infections, such as the flu and pneumonia.

## Bone loss. Bone-building medicines might help prevent bone loss.

## Anemia. Medicines can increase the number of red blood cells in the blood. This can help relieve ongoing anemia.

# Can Multiple Myeloma Be Prevented?

## There is no sure way to prevent multiple myeloma. But there might be things you can do to help lower your risk.

## Lowering your risk of multiple myeloma

## Most of the risk factors for multiple myeloma, like your age and family history, can’t be changed or controlled. But there are things you can do that might help lower your risk:

## Get to and stay at a healthy weight.

## If possible, avoid radiation and chemicals that might raise multiple myeloma risk.

## MGUS and the risk of myeloma

## Some people are known to be at increased risk of myeloma. This includes people with monoclonal gammopathy of undetermined significance (MGUS). At this time, there is no known way to prevent people with MGUS from getting multiple myeloma, but this is an active area of research.

## **Epidemiology**

MM accounts for 10% of all hematologic cancers. The American Cancer Society estimates that in the United States, approximately 36,110 new cases of MM (20,030 in men and 16,080 in women) will be diagnosed in 2025.The lifetime risk of getting MM is approximately 1 in 108 for men and 1 in 133 for women (overall, 0.8%).Approximately 12,030 deaths from MM (6540 in men and 5490 in women) are expected to occur in the US in 2025.Rates for new MM cases rose slightly over the last decade, from 7.0 per 100,000 persons in 2011 to 7.1 per 100,000 persons in 2021, while death rates declined slightly, from 3.4 to 2.8 per 100,000 from 2012 to 2022.

In the US, the annual incidence of MM per 100,000 persons is 8.1 cases in White men, 5.1 cases in White women, 17.1 cases in Black men, and 13.0 cases in Black women. For Hispanics, the rates are 7.9 in men and 5.8 in women. Rates are lowest for Asians/Pacific Islanders, at 5.1 in men and 3.3 in women.According to a study of the ethnic disparities among patients with MM, Hispanics had the youngest median age at diagnosis (65 years) and Whites had the oldest (71 years).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for many of the vague symptoms accompanying multiple myeloma is broad. However, several entities must be considered and ruled out before diagnosis and treatment. Following is a list of important diseases to consider and how to differentiate these from multiple myeloma:

**Monoclonal Gammopathy of Undetermined Significance (MGUS)**

* Serum monoclonal protein less than 3 g/dl
* Clonal bone marrow plasma cells less than 10%
* No end-organ damage

**Smoldering Multiple Myeloma**

* Monoclonal protein is greater than or equal to 3 g/dl
* Clonal bone marrow plasma cells between 10% to 59%
* No end-organ damage

**Solitary Plasmacytoma**

* Solitary lesion made up of clonal plasma cells
* Normal bone marrow
* Negative imaging outside of the single lesion
* No end-organ damage

**Waldenstrom Macroglobulinemia**

* Lymphoplasmacytic lymphoma noted in the bone marrow
* The type of M protein is IgM which is very unusual in MM.
* Presence of MYD88 L265P
* Symptoms include hyperviscosity, peripheral neuropathy, anemia, lymphadenopathy, and hepatosplenomegaly

**AL Amyloidosis**

* Caused by deposition of amyloid fibrils or non-fibrillar material resulting in heart failure, hepatomegaly, and/or nephrotic syndrome
* Less than 20% plasma cells in the bone marrow and lack of lytic lesions
* Congo-red staining on bone marrow or affected tissue

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