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Myeloproliferative Neoplasms: In Detail

Revised **2025**

Formerly titled Myeloproliferative Neoplasms: Polycythemia Vera, Essential Thrombocythemia and Myelofibrosis

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Myeloproliferative Neoplasms: In Detail

Polycythemia Vera, Essential Thrombocythemia and Myelofibrosis

Contents

Acknowledgement

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Introduction

Myeloproliferative neoplasms (MPNs) are a heterogeneous (diverse) group of blood cancers in which the bone marrow overproduces one or more types of blood cells — red blood cells, white blood cells and platelets. Myeloproliferative neoplasms usually develop slowly over time, and different types of MPNs affect different types of blood cells. These blood cancers are also called "myeloproliferative diseases" and "chronic myeloproliferative neoplasms."

There are several types of MPNs, three of which are traditionally grouped together because of their shared features. These three are often referred to as "classic" MPNs or "Philadelphia-negative classical" MPNs. They are:

- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Myelofibrosis (MF)

This booklet focuses on the symptoms, diagnosis and treatment of these "classic" MPNs. It also includes brief descriptions of blood and bone marrow in normal conditions, as well as definitions of health terms related to these diseases to help readers understand them. The more you know about your disease, the better you can take care of yourself — your mind, your body and your health.

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Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are a group of blood cancers in which too many blood cells are made in the bone marrow. Bone marrow is the spongy tissue inside the large bones of the body.

- "Myelo" refers to bone marrow
- "Proliferative" means to grow or reproduce quickly
- "Neoplasm" is an abnormal growth of cells and an alternative term for cancer

There are several types of MPNs. Different MPNs affect different blood cells. Each MPN has specific criteria for its diagnosis. Some MPNs are indolent (slow growing), while others are more aggressive.

1. **Polycythemia vera (PV)** causes an excess of red blood cells but can also be associated with an increase in white blood cells and platelets
2. **Essential thrombocythemia (ET)** causes an excess of platelets alone
3. **Myelofibrosis (MF)** causes an excess of megakaryocytes (platelet-forming cells) and other myeloid cells that leads to a buildup of scar tissue (known as fibrosis) in the bone marrow. The bone marrow fibrosis lowers the production of red blood cells and platelets over time.

Other types of MPNs include:

- Chronic myeloid leukemia (CML) – an increase in myeloid cells driven by a specific chromosomal abnormality called the Philadelphia chromosome (BCR::ABL1)
- Chronic neutrophilic leukemia (CNL) – A disorder in which there are too many neutrophils (a type of white blood cell) in the blood. The excess neutrophils may cause the spleen and liver to become enlarged. May remain stable for many years, or it may progress quickly to an acute form of leukemia.
- Chronic eosinophilic leukemia (CEL) – A disorder in which there are too many eosinophils (a type of white blood cell) in the bone marrow, blood and other tissues. May progress slowly over many years, or quickly to an acute form of leukemia.
- MPN unclassified (MPN-U) – an MPN subtype that does not fall clearly into the other subtypes above

These other types of MPNs are not covered in this booklet. Visit www.LLS.org/booklets to see the free LLS booklets *Chronic Myeloid Leukemia* and *Chronic Neutrophilic Leukemia Facts* for more information about these two diseases.

Normal Blood Cell Development. Blood cells form in the bone marrow, where they begin as immature, underdeveloped cells called "hematopoietic (blood) stem cells." In healthy bone marrow, these blood-forming cells eventually develop into red blood cells, white blood cells and platelets. Red blood cells carry oxygen throughout the body. White blood cells help fight infections. Platelets help stop bleeding by clumping together (clotting) at the site of an injury. Normal blood cells do not live forever. New blood cells are constantly being made to replace old ones that die. See page 47 for information about normal blood development.

How MPNs Develop. A mutation or a series of mutations acquired during your lifetime (rather than inherited and present at birth) in the DNA (genetic material) of a blood stem cell can cause an MPN. A mutation is any change in the sequence of the DNA of a cell. Genetic mutations may be caused by mistakes during cell division or by exposure to DNA-damaging agents in the environment, such as cigarette smoke or radiation. Gene mutations happen in our cells all the time, but they usually do not affect our health. In many cases, cells detect the changes and are able to repair them. However, some mutations cause cells to divide more rapidly and remain active for longer than normal, which can lead to cancer.

The causes of MPNs are not fully understood. They are complex diseases that may have many contributing factors. Researchers believe proteins known as Janus kinases (JAKs) are involved. These proteins transmit signals within cells that affect the production of blood cells in the bone marrow. They also help control the number of red blood cells, white blood cells and platelets in the bone marrow. When JAKs are working normally, they help the body make the right number of blood cells. But when too many signals are sent by these proteins, it causes too many blood cells to be made in the bone marrow. This is referred to as "overactive JAK signaling."

In MPNs, overactive JAK signaling is thought to be caused by a mutation or series of mutations in the DNA of an immature blood stem cell in the bone marrow. The mutation(s) may be in the genes that code for JAK proteins, or in the genes that affect how they work. As a result, the stem cell reproduces continually, creating more and more abnormal stem cells, which then produce too many blood cells. Myeloproliferative neoplasms usually get worse over time as the number of extra blood cells build up in the bone marrow and bloodstream.

The mutation(s) can also lead to the overproduction of cytokines, in addition to the overproduction of blood cells. Cytokines are proteins that are crucial in controlling the growth and activity of immune-system cells and blood cells. Cytokines are also associated with inflammation. Many patients with MPNs experience symptoms caused by inflammation. Symptoms of inflammation may include unexplained fevers, night sweats, weight loss, itchy skin, fatigue and bone pain.

A majority of MPN patients have an identified "driver mutation" of a gene, such as *JAK2, CALR* or *MPL*. Driver mutations are changes in the DNA sequence of genes that cause cells to become cancerous and to grow and spread in the body. However, not all people with MPNs have an identified driver mutation.

In most cases, the cause of the mutation(s) to the blood stem cell is unknown. While MPNs have been reported in more than one member of the same family, they are generally not considered inherited diseases. Rather, they arise from gene mutations that occur during a person's lifetime, called "acquired (or somatic) mutations."

Often other mutations called "subclonal mutations" can be detected in patients with MPNs and more so in MF. Some of these mutations are known to have prognostic implications and can be categorized as high molecular risk (HMR) such as *EZH2, ASXL1, IDH1/2,* and *U2AF1*. These mutations can also be included in newer prognostic models.

- Polycythemia vera is associated with mutations in the *JAK2* gene, although other mutations may play a role as well. Approximately 95 percent of patients who have PV have a mutation of the *JAK2* gene.
- About 90% of patients with ET have a mutation of the *JAK2, MPL* or *CALR* gene, although other mutations may play a role in the disease as well. These genes provide instructions for making proteins that promote the growth and division of megakaryocytes (platelet-forming cells). Mutation of these genes increases the production of megakaryocytes, which in turn results in an increased number of platelets. When none of these mutations are detected, the term "triple negative" is used.
- Most patients with MF have a *JAK2* (most common), *CALR* or *MPL* mutation. About 10 percent of patients with MF do not have any of these three mutations. In these cases, the disease is described as "triple negative."

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of disease. A "sign" is a change the doctor sees during an exam or in a laboratory test result. A "symptom" is a change a patient can see and/or feel.

A person who has signs or symptoms that suggest the possibility of a myeloproliferative neoplasm (MPN) is referred to a specialist called a

hematologist-oncologist. This is a doctor who has special training in diagnosing and treating blood disorders and blood cancers such as leukemia, lymphoma and myeloma. In some large medical centers, there are hematologist-oncologists who specialize in treating MPNs.

Signs and Symptoms of Polycythemia Vera (PV). Polycythemia vera develops slowly and may not cause symptoms for many years. In many cases, PV is diagnosed based on a blood test done for another reason, even before symptoms occur. Reduced blood flow due to high numbers of red blood cells and the enlargement of the spleen are what cause a patient's symptoms.

Signs and symptoms of PV may include:

- Fatigue (tiredness)
- Pruritus (itchy skin) especially after warm baths or showers (aquagenic pruritus)
- Erythromelalgia (redness, pain and burning feeling on the skin of the face, hands or feet)
- Headaches, dizziness and weakness
- Difficulties concentrating
- Night sweats
- Insomnia
- Blurred vision, double vision or seeing dark or blind spots that come and go
- Tinnitus (high pitch ringing in the ears)
- Shortness of breath
- Angina (chest pain)
- Weakness
- Dizziness
- Excessive bleeding or bruising
- Peripheral neuropathy (numbness, tingling or burning sensation in the feet)
- Swelling and pain in the stomach
- Feeling full after eating a small meal
- Unexplained weight loss
- Bone pain in long bones and most often the legs

Signs and Symptoms of Essential Thrombocythemia (ET). Essential thrombocythemia develops slowly and may not cause symptoms for years. In many cases, ET is diagnosed based on a blood test done for another reason, even before symptoms occur.

Some of the more serious signs and symptoms of ET are linked to high platelet counts that can cause the development of a thrombus (blood clot). The symptoms include:

- Pain, swelling and redness in the arms or legs (due to deep vein thrombosis, a blood clot that develops in a vein deep inside the body)
- Shortness of breath, chest pain and cough (due to a pulmonary embolism, a blood clot in the lungs)
- Chest pain, shortness of breath and nausea (due to a heart attack caused by a blood clot)

If a blood clot occurs in the arteries that supply blood to the brain, it may cause a temporary loss of blood flow to part of the brain. This can cause a stroke or a transient ischemic attack (TIA), with signs and symptoms that include:

- Headaches
- Dizziness
- Weakness or numbness on one side of the body
- Blurred or double vision
- Slurred speech

In a small number of patients with ET who have an extremely high platelet count, the disease may cause bleeding. Signs and symptoms of bleeding may include:

- Easy bruising
- Nosebleeds
- Gastrointestinal (GI) bleeding
- Bloody stools
- Blood in the urine

Other signs and symptoms of ET include:

- Fatigue
- Sleep problems
- Weight loss
- Low-grade fevers
- Night sweats
- Peripheral neuropathy (numbness, tingling or burning sensation in the feet)
- Sexual problems

- Erythromelalgia (redness, pain and burning feeling on the skin of the face, hands or feet)
- Feeling full after eating a small meal
- Abdominal discomfort due to an enlarged spleen

Signs and Symptoms of Myelofibrosis (MF). Myelofibrosis usually develops slowly and often does not cause symptoms early on. Because of this, it may be discovered during a routine blood test done for another reason before symptoms of MF occur.

When fibrosis develops in the bone marrow (due to the excessive production of megakaryocytes and other myeloid cells), the bone marrow is unable to produce enough normal blood cells. The lack of healthy blood cells causes many of the signs and symptoms of MF. These include:

- Fatigue, weakness, shortness of breath or pale skin due to a low red blood cell count
- Frequent infections due to a low white blood cell count
- Bleeding or bruising easily due to a low platelet count
- Abdominal pain, feeling of fullness, decreased appetite and weight loss as a result of splenomegaly (an enlarged spleen) or hepatomegaly (enlarged liver)
- Night sweats
- Pruritus (itchy skin)
- Fever
- Bone or joint pain

Symptom Assessment. Reducing symptoms is a key goal of treatment. Therefore, it is important to take an active role in monitoring your symptoms. Careful tracking of your symptoms can help you and your doctor better understand how to manage and modify your care over time.

One tool you and your doctor can use to evaluate your symptoms is the Myeloproliferative Neoplasm Symptom Assessment Form, also known as the MPN10 (see **Table 1** on page 10). This form measures 10 symptoms, each on a scale from 0 to 10. Higher scores indicate more severe symptoms.

This form can be used to track your symptoms and monitor how you are feeling over time. It is recommended that the symptoms of all patients with an MPN be assessed both before and during treatment. Worsening symptoms can be a sign of disease progression. The MPN10 can help your doctor assess and track symptom progression and severity as well as guide care management and treatment plans.

You can find an online version of this assessment form at https://thehematologist.org/mpn-total-symptom-score

Table 1. Myeloproliferative Neoplasm Symptom Assessment Form
(Recommended for monitoring symptoms during the course of treatment)

Symptom	Circle 0 if None or Absent Circle 10 if Worst Imaginable										
Please rate your fatigue (weariness, tiredness) circle the one number that describes your WORST level of fatigue during the past 24 hours	0	1	2	3	4	5	6	7	8	9	10
Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms											
Filling up quickly when you eat (early satiety)	0	1	2	3	4	5	6	7	8	9	10
Abdominal discomfort	0	1	2	3	4	5	6	7	8	9	10
Inactivity	0	1	2	3	4	5	6	7	8	9	10
Problems concentrating-compared to before MPN diagnosis	0	1	2	3	4	5	6	7	8	9	10
Night sweats	0	1	2	3	4	5	6	7	8	9	10
Itching (pruritus)	0	1	2	3	4	5	6	7	8	9	10
Bone pain (widespread, not joint pain or arthritis)	0	1	2	3	4	5	6	7	8	9	10
Fever (>100°F)	0	1	2	3	4	5	6	7	8	9	10
Unintentional weight loss last 6 months	0	1	2	3	4	5	6	7	8	9	10

Abbreviation: MPN, myeloproliferative neoplasm

Sources: Association of Community Cancer Centers. Advancing Care for Patients with Myeloproliferative Neoplasms. Landscape Analysis 2023.; National Comprehensive Cancer network© (NCCN©) NCCN Guidelines Version 2.2024 – August 8, 2024. Myeloproliferative Neoplasms.; National Comprehensive Cancer network© NCCN Guidelines for Patients© Myeloproliferative Neoplasms, 2024.

Complications

In medicine, a complication is a medical problem that occurs during the course of a disease or after a procedure or treatment. Myeloproliferative neoplasm (MPN) patients have an increased risk for cardiovascular complications, including heart failure, thrombosis (blood clots) and pulmonary hypertension, depending on the form of MPN and the mutations associated with it. They can also experience complications due to organ enlargement or damage caused by the disease. Sometimes an MPN can progress or transform into another form of blood cancer.

Abnormal Blood Clots. People with MPNs have an increased risk of abnormal bleeding that can range from mild to life threatening.

- **Thrombus (blood clot).** People with MPNs have an increased risk of developing abnormal blood clots. These diseases slow down blood flow due to an abnormal increase in blood cells. Blood clots are the most frequent, sometimes life-threatening, complication of polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF). When blood clots form in an artery, they can lead to a heart attack or a stroke. Deep vein thrombosis (DVT) occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body, usually in the legs. This can cause pain, swelling and reddening in the affected area. If a blood clot from a deep vein breaks loose and travels to the lungs, it can become lodged in the lungs and block blood flow, causing a serious blockage called a "pulmonary embolism." Symptoms of a pulmonary embolism include shortness of breath, chest pain and cough.
- **Stroke and heart attack.** If a blood clot occurs in the arteries that supply blood to the brain, it may cause a stroke (a loss of blood flow to part of the brain, which damages brain tissue) or a transient ischemic attack (TIA) (a type of stroke that only lasts a few minutes when the blood supply to part of the brain is briefly blocked). If a clot blocks blood flow to the heart, it can cause a heart attack. Without blood, the affected heart tissue can lose oxygen and die. Symptoms of a heart attack include pain in the chest, neck or back, as well as fatigue, dizziness and an abnormal heartbeat.
- **Bleeding.** Usually, bleeding is related to low platelet counts in people with advanced MF. In contrast, a very high platelet count, which occurs in patients with ET, can also increase the risk of bleeding because an excess number of platelets can alter the normal process of clotting in the blood. Patients with PV may develop acquired von Willebrand disease, a clotting disorder that puts them at a high risk of bleeding. In addition, some medications to treat MPNs can cause bleeding if they decrease the platelet counts to a very low level. People on blood thinners as treatment for an abnormal blood clot are at risk of bleeding as well. MPN patients need to discuss bleeding concerns with their doctors when planning to have surgery or another medical procedure.

Other Complications

- **Enlarged spleen.** The spleen is an organ located on the left side of the upper abdomen, near the stomach and below the rib cage. It filters the blood, stores blood cells and destroys old blood cells. The spleen may become abnormally enlarged in people with MPNs because it is working harder to manage the increased number of blood cells. An enlarged spleen can cause discomfort or pain in the abdomen. When the spleen pushes up against the stomach, it may also cause a feeling of being full along with a decreased appetite. This complication can occur in people with PV and ET, but it is more common in patients who have MF.
- **Extramedullary hematopoiesis.** When the bone marrow is no longer able to make enough blood cells, other organs in the body, such as the spleen and the liver, may begin to produce blood cells. This is called "extramedullary hematopoiesis," and it often causes the spleen and/or liver to become enlarged.

It may also cause developing blood cells to form clumps or tumors in other areas of the body. This complication may occur in patients with MF or in patients with PV or ET that progresses to MF. Extramedullary hematopoiesis may cause bleeding in the gastrointestinal (GI) system, coughing or spitting up blood, compression of the spinal cord or seizures.

- **Bone and joint pain.** Myelofibrosis may lead to fibrosis of the bone marrow and inflammation of the connective tissue that surrounds the bones, resulting in severe bone and joint pain and tenderness.
- **Gout.** This condition is marked by increased levels of uric acid in the blood, joints and tissues. Myelofibrosis increases the body's production of uric acid. When uric acid builds up, it forms crystals in the joints that cause sharp pain, swollen joints and inflammation.
- **Portal hypertension.** Normally, blood flows from the spleen into the liver through a large blood vessel called the "portal vein." When the spleen is enlarged, increased blood flow through the portal vein can lead to high blood pressure in the vein. This can force excess blood into smaller veins in the stomach and esophagus, potentially causing these veins to rupture and bleed. Portal hypertension may also be caused by a blood clot that develops in the portal vein, which may obstruct blood flow through it. This is a rare complication that can occur in people with PV, ET and MF.
- **Transformation to another blood cancer.** In a small percentage of patients, an MPN may sometimes progress to acute myeloid leukemia (AML) and, less commonly, to myelodysplastic syndrome (MDS). Leukemic transformation in MPNs (also known as "blast-phase MPN") has an estimated incidence (the number of new cases of a disease diagnosed each year) of 3-7% for PV, 1-4% for ET and 9-13% for primary MF.

Testing for Myeloproliferative Neoplasms

While certain signs and symptoms may indicate a person has a myeloproliferative neoplasm (MPN), a series of tests are needed to confirm the diagnosis. It is important to have an accurate diagnosis, as it helps the doctor to:

- Estimate how the disease will progress
- Determine the appropriate treatment

Talk to your doctor about:

- The diagnostic tests that are being done
- What the results mean
- Getting copies of the test results

To diagnose an MPN, doctors use a variety of tests to analyze blood and bone marrow cells. A pathologist—a doctor who specializes in identifying diseases by studying cells under a microscope—will examine the blood cells and the bone marrow cells. The samples should also be examined by a hematopathologist, a pathologist who specializes in diagnosing blood and bone marrow diseases.

The following are some of the tests done to diagnose an MPN. Some of these tests may be repeated both during and after treatment to evaluate if the treatment is working. Visit www.LLS.org/educationvideos to learn more about these different types of tests. Visit www.LLS.org/booklets to view *Understanding Lab and Imaging Tests.*

Medical History. If a person has signs or symptoms of an MPN, the doctor will take a detailed medical history and physical examination. The medical history should include information about the patient's:

- Cardiovascular risk factors, such as high blood pressure and diabetes
- Past illnesses and injuries
- Current and past medications, supplements, surgeries and blood transfusions
- History of a thrombus (blood clot) or a hemorrhagic event (loss of blood from damaged blood vessels)
- Medical history of blood relatives (because some illnesses run in families)
- Current symptoms

Physical Examination. After completing the medical history, the doctor will conduct a physical examination. During the exam, the doctor may listen to your lungs and heart, carefully examine your body for signs of infection and disease and check your vital signs (blood pressure, heart rate and temperature). The doctor may also feel different parts of your body and check to see if the organs are of normal size, are soft or hard or cause pain when touched. For example, the doctor may feel your abdomen to see if you have an enlarged spleen or liver.

Complete Blood Count (CBC) with Differential. This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin (a protein inside red blood cells that carries oxygen from the lungs to tissues in the body) and the hematocrit (the percentage of whole blood made up of red blood cells). The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

- People with polycythemia vera (PV) have high red blood cell counts. They also often have increased hemoglobin levels, increased hematocrit levels, increased white blood cell counts and increased platelet counts
- In patients with essential thrombocythemia (ET), the platelet count is usually higher than normal
- People with myelofibrosis (MF) often have an abnormally low level of red blood cells. Their white blood cell count is usually higher than normal but in some cases, it is lower than normal. The platelet count may be higher or lower than normal.

Red Cell Mass Test. This test measures the volume (amount) of red blood cells in relation to the volume of plasma (fluid) in whole blood.

In patients with PV, there may be an absolute increase in red blood cell mass. This test is performed infrequently in the United States due to the high cost, difficulty obtaining the appropriate test materials and the availability of other tests that can be used to diagnose PV, such as molecular tests (see Next-Generation Sequencing (NGS) on page 19).

Peripheral Blood Smear. In this procedure, a sample of peripheral blood (the blood that circulates throughout the body in the arteries, capillaries and veins) is viewed under a microscope. The pathologist looks to see the number of different types of blood cells and if there are any unusual changes in the size, shape or appearance of various types of blood cells.

- In patients with ET, the platelets in the sample may appear enlarged or clumped together. The test also checks for the presence of immature cells, called "blast cells," in the blood. Blast cells are normally found in the bone marrow but are not typically found in the peripheral blood of healthy individuals.
- People with MF often have abnormal, teardrop-shaped red blood cells as well as immature blast cells in their blood.

Blood Chemistry Profile. A group of blood tests that measure the levels of certain substances released into the blood by organs and tissues in the body. These substances include electrolytes (such as sodium, potassium and chloride), fats, proteins, glucose (blood sugar), uric acid and enzymes. The test findings indicate how well a person's kidneys, liver and other organs are working. Although this test is not used to diagnose an MPN, results showing an abnormal amount of a particular substance in the blood may be a sign of disease or some other health problem.

Lactate dehydrogenase (LDH). This is a protein, normally present in most cells, which is released into the blood when a cell is damaged. A high level of LDH in the blood is a reflection of the amount of diseased cells being produced and dying.

Uric Acid Test. This test measures the amount of uric acid in the body. When cancer cells break down and die, they release their contents into the blood. If the cancer cells break down too quickly, the kidneys cannot remove these substances from the blood. An increased level of uric acid can lead to tumor lysis syndrome (TLS). See page 37 for more information about TLS.

People with MF often have elevated serum levels of uric acid and LDH. During certain stages, MF causes many blood cells to die. Dying blood cells release LDH and uric acid.

Blood Clotting Tests. Patients with very high platelet counts may be tested for acquired von Willebrand disease, a blood disorder that can impair normal blood clotting and cause major bleeding. Blood contains many proteins that help the body stop bleeding, one of which is known as von Willebrand factor. High platelet counts can limit how well the von Willebrand proteins clot. Several blood clotting tests are used to diagnose von Willebrand disease.

Polycythemia vera patients with very high platelet counts may develop acquired Von Willebrand disease. They are at increased risk of bleeding.

Erythropoietin (EPO) Level. This test measures the level of erythropoietin (EPO) in the blood. EPO is a hormone primarily made in the kidneys to stimulate the production of new red blood cells.

In people with PV, high red blood cell counts can suppress EPO levels. Results of EPO tests can be used to help diagnose PV.

Bone Marrow Aspiration and Biopsy. Both of these procedures remove bone marrow cells and test them for abnormalities. They are generally done at the same visit, either at the doctor's office or in a hospital. After medicine has been given to numb the skin and the surface of the bone, the aspiration and biopsy samples are taken separately, using two different needles. The samples are removed from the patient's pelvis or "hip bone," generally from the area right above the buttocks.

Bone marrow has both a solid and liquid component. For a bone marrow aspiration, a special needle is inserted through the hip bone and into the bone marrow to remove a liquid sample of cells. For a bone marrow biopsy, a wider needle is used to remove a sample of solid bone that contains bone marrow. See **Figure 1** on page 16 for more information on blood and bone marrow tests.

Figure 1. How Are the Blood and Bone Marrow Tests Done?

Blood Test. Blood is taken from the patient's arm with a needle. The blood is collected in tubes and sent to a lab for testing.

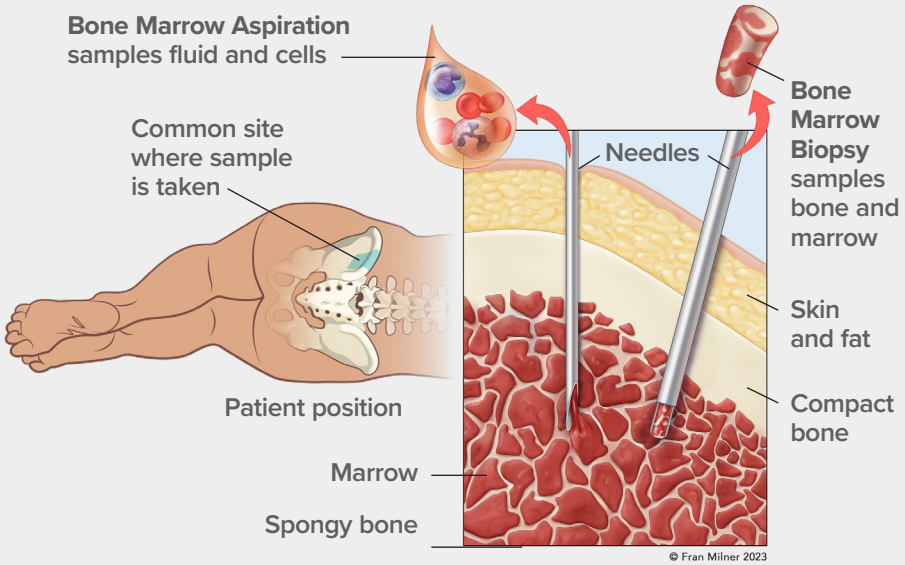
Bone Marrow Aspiration. A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

Bone Marrow Biopsy. A very small amount of bone filled with marrow cells is taken from the body and sent to a lab for testing.

Both bone marrow tests are done with special needles. Some patients are awake for the procedure. They get medication first to numb the part of the body that will be used to get the sample of cells. The sample of cells is usually taken from the patient's hip bone.

Blood and marrow tests may be done in the doctor's office or in a hospital. Bone marrow aspiration and biopsy are almost always done at the same visit. Blood and bone marrow tests may be done both during and after treatment. The tests are repeated to see if the treatment is working

Bone Marrow Aspiration and Biopsy



Left: The place on the back of the patient's pelvic bone where a bone marrow aspiration or biopsy is done. **Right:** Where the two needles go inside the bone to collect the liquid sample for aspiration (the needle on the left) and the bone sample for biopsy (the needle on the right). The needles are different sizes for each test. These two tests are usually done at the same visit.

Visit www.LLS.org/3D and click on "Bone Marrow Biopsy and Aspiration" to view an interactive 3D model that will help you visualize and better understand the bone marrow aspiration and biopsy procedures.

The samples are then sent to a lab and examined under a microscope to look for the presence of abnormal cells and the occurrence of scar tissue, called "fibrosis," in the bone marrow. This is necessary to help distinguish MF from other types of MPNs.

- Patients with MF typically have an increased number of megakaryocytes (platelet-forming cells) that are unusual in size and shape and fibrosis in the bone marrow. In some patients who have MF, it is not possible to obtain a liquid sample during a bone marrow aspiration due to scarring in the bone marrow. The scarring will cause the aspiration to be "dry," meaning no cells can be obtained for this test.
- Patients with PV have above-normal numbers of blood cells, as well as an abnormal number of megakaryocytes (platelet-forming cells) in the bone marrow. There should not be an excess of fibrosis.
- In patients with ET, there are increased numbers of megakaryocytes (platelet-forming cells) in the bone marrow. These megakaryocytes also appear abnormal in shape and size. There should not be an excess of fibrosis.

Biomarker Testing. These laboratory tests examine the cancer cells from the blood, bone marrow or other tissues to check for certain genes, proteins or other molecules to provide information about a person's cancer. Each person's cancer has a unique pattern of biomarkers.

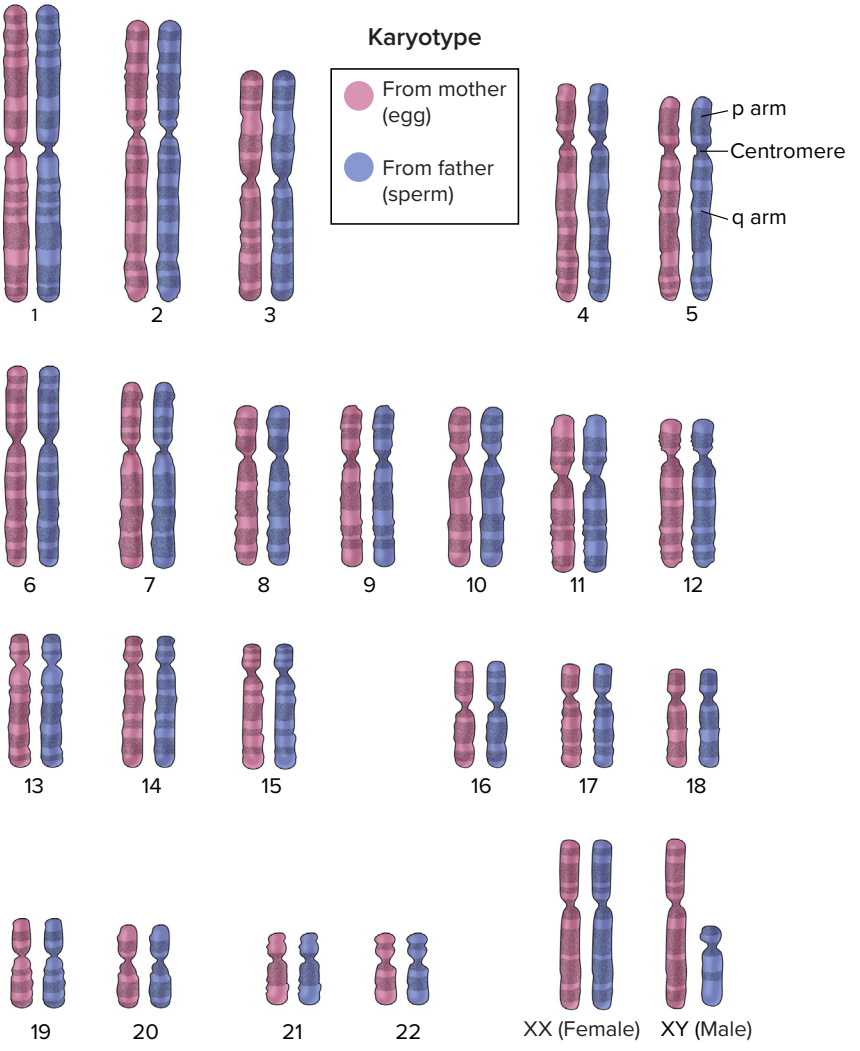
Biomarker testing may also be used to help plan treatment, find out how well treatment is working or predict whether cancer will come back or spread to other parts of the body. Visit www.LLS.org/booklets for the book *Understanding Genetics.* Biomarker tests for MPN include:

Cytogenetic analysis (karyotyping). The process of analyzing the number and size of the chromosomes in cells. It detects chromosome changes and, in some cases, may identify the actual genes that have been affected. Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure. These findings help doctors diagnose specific types of blood cancer, determine the best treatment approaches and monitor a patient's response to treatment.

In some cases of MF, the chromosomes of the cancer cells have abnormal changes that can be seen under a microscope, such as extra or missing chromosomes or broken or rearranged chromosomes. Some patients with MF have a "complex karyotype," which is when there are three or more unrelated abnormalities in the chromosomes.

Fluorescence In Situ Hybridization (FISH). Doctors use this very sensitive test to detect certain abnormal changes in the chromosomes and genes of cancer cells. In the nucleus of most cells, genetic material is packaged into threadlike structures called "chromosomes." Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes. Chromosomes are passed from the parents to a child. Every person inherits 23 chromosomes from their mother's egg cell, and 23 chromosomes from their father's sperm cell. Each pair of chromosomes has a certain size, shape and structure. Each chromosome is divided into two sections or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm."

See the **Figure** below for an illustration of human chromosomes lined up in pairs, an arrangement called a karyotype.



Pieces of DNA that contain special fluorescent dyes are prepared in the laboratory and added to the cancer cells on a glass slide. The pieces of DNA that bind to certain genes or areas of chromosomes light up when the slide is viewed under a specialized "fluorescence" microscope. Not only can FISH identify abnormal chromosome changes that can be seen with a microscope, but it can also detect some changes that are too small to be seen with basic cytogenetic testing. However, FISH is not used as a general screening tool and has one disadvantage—the doctor must select the specific chromosomes or genes to examine before the test is performed.

Polymerase chain reaction (PCR): This is a very sensitive test used to detect and measure specific genetic mutations that are too small to be seen with a microscope. PCR testing basically amplifies (increases) small amounts of specific pieces of DNA so they are easier to detect and measure in a cell sample. It looks for the presence or absence of specific gene mutations. PCR testing can be done with blood or bone marrow samples.

Next-Generation Sequencing (NGS). Next-generation sequencing, also called "molecular testing" or "genomic testing," refers to a number of different laboratory tests that examine the exact sequence (order) of DNA or RNA. This makes it possible to identify a variety of genetic changes in a patient's cancer cells. These changes are important in guiding risk assessment and prognosis and may also inform treatment decisions for targeted therapy specific to the particular change in the genetic sequence of the cancer cell. The information these tests provide can help doctors to determine which patients are at high risk and may need more intensive treatment or may benefit from treatment with new therapies.

There are targeted sequencing tests (also called "multigene panels") that look for specific mutations in the cancer cells. These tests focus on specific sets of genes or areas of DNA. There are also broad DNA sequencing tests (genomic screening tests) that analyze the sequence of large regions of DNA, rather than looking for mutations of specific genes. Doctors may also order sequencing of all the DNA in the cancer cells, and/or normal cells in the body. This test is known as "whole genome sequencing." The term "next-generation sequencing (NGS)" is a catch-all term that describes a number of different modern sequencing technologies. These technologies allow for sequencing of DNA and RNA much more quickly and cheaply than sequencing methods that were used previously.

Next-generation sequencing may be done when the cancer is first diagnosed and is also used after treatment for evaluating measurable residual disease (MRD). It can find one cancer cell among one million normal bone marrow cells.

Visit www.LLS.org/booklets to read *Measurable Residual Disease*, *Understanding Genetics* and *Understanding Lab and Imaging Tests*.

When an MPN is suspected, it is recommended to exclude a diagnosis of chronic myeloid leukemia (CML). The hallmark of CML is the *BCR-ABL1* fusion gene. FISH and PCR are biomarker tests that can detect this gene in either a blood or bone marrow sample. If *BCR-ABL1* is not detected, CML is ruled out.

If PV is suspected, testing for the *JAK2* gene mutation should be performed. The *JAK2 V617F* mutation is found in more than 95 percent of patients who have PV. If a patient does not have a *JAK2 V617F* mutation, then testing should be done for other mutations. About 4 percent of patients who have PV have the *JAK2* exon 12 mutation.

Approximately 90 percent of patients with ET have a mutation of the *JAK2, MPL* or *CALR* gene. The approximate frequencies of these mutations are:

- *JAK2* mutation — 55%
- *CALR* mutation — 25-30%
- *MPL* mutation — 5-7%

About 10 percent of patients who have ET do not have a *JAK2, MPL* or *CALR* gene mutation. In these cases, the disease is referred to as "triple-negative" ET.

Approximately 90 percent of patients with MF have a mutation of the *JAK2, MPL,* or *CALR* gene. The approximate frequencies of these mutations are:

- *JAK2* mutation — 60%
- *CALR* mutation — 20-30%
- *MPL* mutation — 7-10%

About 10 percent of patients who have MF do not have a *JAK2, MPL* or *CALR* gene mutation. In these cases, the disease is referred to as "triple-negative" MF, and it is associated with a worse prognosis (outcome).

Over the last several years, numerous other gene mutations have been identified in patients with primary MF including the genes called *CBL, LNK/SH2B3, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, DNM3TA, SF3B1, SRSF2,* and *U2AF1.* These mutations may occur in addition to *JAK2, CALR* or *MPL* mutations; a person with MF may have several of these mutations at the same time. Scientists are investigating the role that these and other mutations may have in the onset and progression of MF.

HLA (Human Leukocyte Antigen) Typing. This blood test should be performed in patients who are candidates for allogeneic stem cell transplantation (see page 34). HLAs are proteins found on the surface of most cells in the body. These proteins make up the body's tissue type, which varies from person to person. HLAs play an important role in the body's immune response to foreign substances by helping the body distinguish its own cells from foreign cells. An HLA test is done prior to a donor stem cell transplantation to find out if there is a match between the tissue type of the transplant donor and recipient.

Although HLA typing is not used to diagnose MF, it is an important test for patients who have MF if allogeneic stem cell transplantation is being considered as a treatment option.

See page 34 for more information on allogeneic stem cell transplantation.

Diagnostic Criteria. The International Consensus Classification (ICC) and the World Health Organization (WHO) have created standards for the diagnosis of MPNs. These standards include major and minor criteria associated with each disease. Hematopathologists use the results of diagnostic tests to determine if the criteria for an MPN diagnosis have been met.

For a diagnosis of PV to be made, a doctor looks for three major criteria OR two major criteria and one minor criteria in this table.

Table 2. World Health Organization Diagnostic Criteria for Polycythemia Vera (PV)

Polycythemia Vera **Diagnosis requires 3 major criteria OR 2 major criteria + 1 minor criterion**
Major Criteria
1. Very high red blood cell count, usually identified by either A, B, or C below. A. Elevated hemoglobin level • Hemoglobin level greater than 16.5 g/dL in males • Hemoglobin level greater than 16.0 g/dL in females OR B. Elevated hematocrit level • Hematocrit greater than 49 percent in males • Hematocrit greater than 48 percent in females OR C. Increased red cell mass* 2. Bone marrow biopsy showing abnormally high numbers of blood cells in the bone marrow (called “hypercellularity”) based on the person’s age. This includes elevated red blood cell, white blood cell and platelet counts (a condition called “panmyelosis”) and proliferation of mature megakaryocytes (platelet-forming cells) that vary in size and shape 3. Presence of the *JAK2 V617F* or *JAK2* exon 12 gene mutation
Minor Criterion
Very low erythropoietin level

*Red cell mass is the volume of red blood cells in the blood. This nuclear medicine test is not often used to diagnose MPNs. The red cell mass is considered high when it is 25 percent greater than the normal value.

Source: Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical and genomic data. *Blood.* 2022;140(11):1200-1228. doi.10.1182/blood.2022015850

For a diagnosis of ET to be made, all four of the "major criteria" must be met, or the major criteria 1 to 3, plus a minor criterion must be met.

Table 3. World Health Organization Diagnostic Criteria for Essential Thrombocythemia (ET)

Essential Thrombocythemia **Diagnosis requires 4 major criteria OR major criteria 1 to 3 plus + minor criterion**
Major Criteria
1. Platelet count equal or greater than 450 × 10^9 /L 2. Bone marrow biopsy showing an increased number of megakaryocytes (platelet-forming cells) with abnormal nuclei 3. Exclusion of other diseases defined by WHO criteria, such as: • *BCR-ABL1+* chronic myeloid leukemia • Polycythemia vera • Primary myelofibrosis • Myelodysplastic syndromes • Other myeloid neoplasms 4. Presence of *JAK2, CALR* or *MPL* mutation -- About 10% of patients with ET don't have any of these three mutations. In these cases, the MPN is described as "triple negative."
Minor Criterion
Presence of a clonal marker (chromosome abnormality) or no evidence that the disorder is caused by reactive thrombocytosis --- These criteria include the presence of other biomarkers or no underlying cause of the high platelet count. Other possible causes of high platelet counts are low iron, chronic inflammation and medication side effects.

Source: Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical and genomic data. *Blood*. 2022;140(11):1200-1228. doi.10.1182/blood.2022015850

Myelofibrosis is called primary myelofibrosis (PMF) if it's the only type of MPN a patient has had. There are two stages of PMF based on the amount of fibrosis (scarring) that is seen in the bone marrow:

- Prefibrotic PMF (known as early PMF or pre-PMF)
- Overt PMF

The WHO provides different criteria for diagnosing MF based on these two stages. The first criterion of MF is a high number of abnormal megakaryocytes in the bone marrow. The bone marrow in pre-PMF has minimal or no scarring, whereas there is major scarring in overt PMF. In pre-PMF, the number of bone marrow cells is higher than normal, although the production of red blood cells may be low.

Table 4. World Health Organization Diagnostic Criteria for Myelofibrosis (MF)

Primary Myelofibrosis (PMF)
The diagnosis of pre-PMF or overt PMF requires all 3 major criteria + at least 1 minor criterion confirmed by 2 consecutive tests

PMF, early/prefibrotic stage (pre-PMF)

Major Criteria

1. Proliferation of abnormal megakaryocytes, accompanied by fibrosis in the bone marrow, grade <2
2. Exclusion of other diseases defined by WHO criteria, such as:
   - Essential thrombocythemia
   - Polycythemia vera
   - *BCR-ABL1+* chronic myeloid leukemia
   - Myelodysplastic syndromes OR
   - Other myeloid neoplasms
3. Presence of *JAK2, CALR* or *MPL* mutation or another clonal marker (gene mutation) such as genes *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1,* or the absence of reactive myelofibrosis

Minor Criteria

Presence of at least one of the following, confirmed in two consecutive tests:
- Anemia not caused by another condition, or
- White blood cell count greater than or equal to 11×10^9 /L, or
- Palpable enlarged spleen, or
- Lactate dehydrogenase (LDH) level above upper normal limits

PMF, overt fibrotic stage

Major Criteria

1. Proliferation of abnormal megakaryocytes, accompanied by fibrosis in the bone marrow, grade 2 or 3
2. Exclusion of other diseases defined by WHO criteria, such as:
   - Essential thrombocythemia
   - Polycythemia vera
   - *BCR-ABL1+* chronic myeloid leukemia
   - Myelodysplastic syndromes OR
   - Other myeloid neoplasms

Presence of *JAK2, CALR* or *MPL* mutation or another clonal marker (gene mutation) such as genes *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1,* or the absence of reactive myelofibrosis

Presence of at least one of the following, confirmed in two consecutive tests:
- Anemia not caused by another condition, or
- White blood cell count greater than or equal to 11×10^9 /L, or
- Palpable enlarged spleen, or
- Lactate dehydrogenase (LDH) level above upper normal limits, or
- Presence of immature blood cells in the peripheral blood (called "leukoerythroblastosis")

Source: Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical and genomic data. Blood. 2022;140(11):1200-1228. doi.10.1182/blood.2022015850

Treatment Options

New treatments may have been approved since this booklet was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be participating in a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you.

Talk to your doctor about:

- Your treatment options and the results you can expect from treatment
- The possibility of participating in a clinical trial

Choosing a Hospital and Doctor. Polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) are rare blood cancers. It is important to seek treatment in a center with hematologist-oncologists who have experience in the care of patients with these types of cancer.

Visit www.LLS.org/booklets to view *Choosing a Specialist or Treatment Center.*

Oral Drug Adherence. Many MPN drugs are taken orally (by mouth). In this context, the term "adherence" means staying on a set plan or regimen, taking the medication as prescribed—on the right day and at the right time, and reporting side effects to the heathcare team. If patients are not going to an outpatient clinic to receive treatment, it is important to make sure that they continue to take their medications, as prescribed, at home.

Taking a drug by mouth has many benefits, including improved quality of life, convenience and saving time. Unfortunately, poor adherence to a prescribed oral drug regimen can result in the following problems: drug resistance; poor response to therapy; disease progression; more doctor visits, laboratory tests and hospitalizations, and even death.

For additional information about oral drug adherence, including treatment barriers and solutions and strategies to overcome them, see the free LLS booklets *Oral Treatment Adherence Facts* and *A Medication Resource for Blood Cancer Patients.*

Treatment for Polycythemia Vera

New treatments may have been approved since this booklet was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Polycythemia vera (PV) is characterized by the overproduction of red blood cells in the bone marrow. In many cases, the number of white blood cells and platelets also increases. These blood cells build up in the bone marrow and blood, causing it to thicken and flow slower than normal. Serious health problems may arise, such as uncontrolled bleeding and abnormal blood clots. These blood clots can cause a stroke, a heart attack or a blockage in an artery, in the lungs or in a vein deep within a leg or arm muscle.

Without treatment, PV can be life threatening. It is a chronic disease (a disease or condition that usually lasts for a long period of time and may get worse over time). It is not curable but with careful medical supervision, it can usually be managed effectively for many years. The goals of treatment for PV are to reduce the risks of blood clots and to ease symptoms by lowering the number of excess blood cells.

Risk Factors. Treatment decisions for patients with PV are based on the patient's risk for thrombosis (developing blood clots).

The two main risk factors for thrombosis are a history of a previous blood clot and being aged 60 years or older.

Risk Groups	Measures to prevent blood clots
Low Risk – Patients who have PV younger than 60 years with no history of thrombosis.	• Manage cardiovascular risk factors • Low-dose aspirin (80-100 mg per day) • Phlebotomy
High Risk – Patients who have PV 60 years or older and/or have a history of thrombosis.	• Manage cardiovascular risk factors • Low-dose aspirin (80-100 mg per day) • Phlebotomy (to keep hematocrit below 45 percent for males, or 42 percent for females) • Cytoreductive therapy (medications to reduce the number of blood cells) o Hydroxyurea o Ropeginterferon alfa-2b-njft o Peginterferon alfa-2a o Ruxolitinib

Adapted from NCCN Guidelines for Patients. Myeloproliferative Neoplasms, 2024

Treatment Overview. You will work with your doctor to develop a treatment plan. Many treatment options are designed to manage PV by lowering the hematocrit level below 45 percent for males, or 42 percent for females. Careful medical supervision and therapy is important to keep the hematocrit at a normal level.

Low-Dose Aspirin. Taking low-dose aspirin daily may reduce the risk of blood clots, heart attacks and strokes. It also helps prevent platelets from sticking together, making it less likely for blood clots to form. Low-dose aspirin consists of 80-100 milligrams of aspirin per day. The most common side effects of aspirin are upset stomach and heartburn.

Phlebotomy. Most patients who have PV have their blood drawn regularly to reduce the number of blood cells and decrease blood volume. Phlebotomy is a procedure in which blood is taken from a vein similarly to what is done when donating blood. After phlebotomy, the blood is thinner and less likely to cause "sludging" (which occurs when red blood cells build up along walls of blood vessels). The immediate effect of phlebotomy is to decrease certain symptoms, such as headaches, itchiness, vision problems, ringing in the ears and dizziness.

Drug Therapy. High-risk category patients who have PV may be prescribed cytoreductive drugs to reduce the number of blood cells. Signs that cytoreductive therapy may be needed include a new blood clot, major bleeding, frequent phlebotomy treatments, enlarged spleen, high platelet count, high white blood cell count and/or worsening symptoms. Treatments may include:

- Hydroxyurea (Hydrea®)
- Ruxolitinib (Jakafi®)
- Ropeginterferon alfa-2b-njft (Besremi®)
- Peginterferon alfa-2a (Pegasys®).

See **Table 5** on page 42 and **Table 6** on page 43 for a list of medications used to treat myeloproliferative neoplasms (MPNs) including PV.

Managing Blood Clots. Patients with PV have an increased risk of blood clots compared with the general population. Your doctor may use imaging tests such as ultrasound, CT scans and MRI scans to look for blood clots in your body. If you have a blood clot, your doctor may prescribe an anticoagulant (blood thinner) such as low-molecular-weight heparin. Another option is an oral blood thinner, taken by mouth, such as warfarin. For life-threatening blood clots that have already formed, drugs called "thrombolytics" can be given to dissolve them.

Managing Cardiovascular Risk Factors. Patients with PV should focus on their overall health. A heart-healthy lifestyle may decrease the risk of thrombosis. Lifestyle changes may include:

- **Controlling your blood pressure.** High blood pressure is a major risk factor for heart disease. It is important to get your blood pressure checked regularly and take steps to prevent or control high blood pressure.

- **Keeping your cholesterol under control.** A high cholesterol level in the blood can clog arteries and raise your risk of a heart attack. Lifestyle changes and medicines, if needed, can lower your cholesterol level.
- **Managing diabetes.** Having diabetes increases your risk of heart disease. It is important to get tested for diabetes, and if you have it, to keep it under control.
- **Not smoking.** Patients who smoke should stop smoking, because tobacco causes narrowing of the blood vessels and can increase the risk of heart attacks and strokes.
- **Working toward a healthy body weight.** Being overweight or obese increases the risk of developing high blood pressure, type 2 diabetes and coronary heart disease.
- **Taking your medications.** You may need medications to lower blood pressure and cholesterol and to control diabetes. It is important to take these medications as prescribed by your doctor so you can decrease your chance of having a heart attack or stroke.
- **Exercising.** Moderate exercise such as walking can improve blood flow, which decreases the risk of blood clots. Doing leg and ankle stretches and related exercises can also improve blood circulation and help stop clots from forming in the veins of the legs. A doctor or physical therapist can recommend an exercise plan.

Visit www.LLS.org/nutrition to receive nutrition education and to schedule a free consultation with a registered dietitian.

Treatments to Reduce Itching. A troublesome symptom that occurs in many patients who have PV is itchy skin, a condition called "pruritus." To help prevent itchiness, it is suggested that patients bathe less frequently, and also use cool water and a gentle soap for baths and showers. Hot tubs, heated whirlpools and hot showers or baths should be avoided. It is also important to keep the skin well moisturized with lotion and to try not to scratch it, as that can damage the skin.

If home remedies do not ease your itchy skin and especially if you are having trouble sleeping, your doctor may recommend prescription medications or other treatments to control itching. These may include:

- Antihistamines, such as diphenhydramine (Benadryl®), which may help with itching that does not go away.
- Light therapy (phototherapy), using a medicine called "psoralen" combined with ultraviolet A (UVA) light.
- Medications such as gabapentin or pregabalin that block neurotransmitters in the central nervous system from sending signals that trigger itching

Treatment Outcomes. In some people with PV, the disease remains stable for many years. In many people, life expectancy is the same as it would be if they did not have PV. With careful medical supervision and therapy, PV can usually be

managed effectively for a long time. In some cases, however, it may progress to another type of blood disease, such as myelofibrosis or acute myeloid leukemia.

It is important to know that outcome data can show how groups of people with an MPN responded to treatment in the past, but it cannot always determine how any particular person will respond. For these reasons, patients are advised to discuss information about survival with their doctors.

Treatment for Essential Thrombocythemia

New treatments may have been approved since this booklet was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Essential thrombocythemia (ET) is characterized by the overproduction of thrombocytes (platelets). High numbers of platelets may lead to the formation of blood clots that form in blood vessels. This can cause serious health problems such as a stroke, heart attack or pulmonary embolism. Abnormal bleeding, such as nose bleeds, bleeding gums or bleeding in the gastrointestinal tract, may also occur in patients with a very high number of platelets. Decisions about treatment for ET are based on the patient's risk for developing blood clots.

Risk Factors. The International Prognostic Score for ET (IPSET) groups patients into four risk categories: very low risk, low risk, intermediate risk and high risk.

The treatment approach for ET is based on the patient's risk category, as summarized in the box below.

Risk Category	Measures to prevent blood clots
Very low risk: • 60 years of age or under • Never had a blood clot • No *JAK2* mutation	• Manage cardiovascular risk factors • Low-dose aspirin, if experiencing symptoms caused by low blood flow (headaches, blurred vision)
Low risk: • 60 years of age or under • Never had a blood clot • *JAK2* mutation	• Manage cardiovascular risk factors • Low-dose aspirin
Intermediate risk: • Older than 60 years of age • Never had a blood clot • No *JAK2* mutation	• Manage cardiovascular risk factors • Low-dose aspirin
High risk: • Older than 60 years of age • Had a blood clot • *JAK2* mutation	• Manage cardiovascular risk factors • Low-dose aspirin • Cytoreductive therapy to reduce blood counts: o Hydroxyurea o Peginterferon alfa-2a o Anagrelide

Adapted from NCCN Guidelines for Patients. Myeloproliferative Neoplasms, 2024

Drug Therapy. Treatment for ET includes medications that reduce the risk of clotting complications and reduce the number of blood cells in the bone marrow, especially reducing the platelet count. For some patients with no signs of the disease at the time of diagnosis (other than an increased platelet count), the risk of complications may be low and therefore no treatment is initially needed. However, patients at high risk for blood clots and bleeding may be prescribed medication right away to reduce their platelet counts.

See **Table 5** on page 42 and **Table 6** on page 43 for a list of medications used to treat myeloproliferative neoplasms (MPNs) including ET.

Plateletpheresis. This is a procedure in which blood is drawn from a vein and passed through a machine that separates out and collects just the platelets. The remaining blood components are returned to the patient's bloodstream. It is used only in emergency situations, such as acute clotting complications, when the platelet count is very high and needs to be reduced quickly. The platelet-reducing effect of this therapy is temporary.

Managing Blood Clots. Patients with ET have an increased risk of blood clots compared with the general population. Your doctor may use imaging tests such as ultrasound, CT scans and MRI scans to look for blood clots in your body. If you have a blood clot, treatment depends on where the blood clot is located and how likely it is to harm you. Your doctor may prescribe an anticoagulant (blood thinner) to help prevent blood clots from forming. Low-molecular-weight heparin is a class of blood thinners that can be safely self-injected by the patient at home. Another option is an oral (taken by mouth) blood thinner such as warfarin. For life-threatening blood clots that have already formed, drugs called "thrombolytics" can be given to dissolve them. Any patient who develops a venous blood clot (blood clot in a vein) requires lifelong treatment with anticoagulants.

Managing Cardiovascular Risk Factors. Patients with ET should focus on their overall health. A heart-healthy lifestyle may decrease the risk of thrombosis. Lifestyle changes may include:

- **Controlling your blood pressure.** High blood pressure is a major risk factor for heart disease. It is important to get your blood pressure checked regularly and take steps to prevent high blood pressure or control it.
- **Keeping your cholesterol under control.** A high cholesterol level in the blood can clog arteries and raise your risk of a heart attack. Lifestyle changes and medicines, if needed, can lower your cholesterol level.
- **Managing diabetes.** If you have diabetes, it increases your risk of heart disease. It is important to get tested for diabetes and to keep it under control.
- **Not smoking.** Patients who smoke should stop smoking, since tobacco causes narrowing of the blood vessels and can increase the risk of heart attacks and strokes.

- **Working toward a healthy body weight.** Being overweight or obese increases the risk of developing high blood pressure, type 2 diabetes and coronary heart disease.
- **Taking your medications.** Some patients may need medications to lower blood pressure and cholesterol and to control diabetes. It is important to take these medications as prescribed by your doctor in order to decrease the chance of having a heart attack or stroke.
- **Exercising.** Moderate exercise such as walking can improve blood flow and decrease the risk of blood clots. Doing leg and ankle stretches and exercises can also improve blood circulation and help stop clots from forming in the veins of the legs. A doctor or physical therapist can recommend an exercise plan.

Visit www.LLS.org/nutrition to receive nutrition education and to schedule a free consultation with a registered dietitian.

Treatment Outcomes. On average, people with ET have a normal to near-normal life expectancy, if they are properly monitored and treated. In very rare cases, ET transforms into a more aggressive blood disease. In a small number of patients, it transforms into myelofibrosis, and less frequently into acute myeloid leukemia or an MPN.

It is important to know that outcome data can show how groups of people with an MPN responded to treatment in the past, but it cannot always determine how any particular person will respond. For these reasons, patients are advised to discuss information about survival with their doctors.

Treatment for Myelofibrosis

New treatments may have been approved since this booklet was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Myelofibrosis (MF) is characterized by the buildup of scar tissue, called “fibrosis,” in the bone marrow. As scar tissue increases, the bone marrow cannot make enough healthy blood cells.

When myelofibrosis develops on its own (and not as the result of another bone marrow disease) it is called “primary myelofibrosis” (PMF). When another myeloproliferative neoplasm (MPN), such as polycythemia vera (PV) or essential thrombocythemia (ET), transforms into MF, it is known as “secondary MF,” also called “post-PV MF” or “post-ET MF.” Between 10 and 20 percent of all MF cases begin as either PV or ET.

Over time, the fibrous tissue impairs the bone marrow’s ability to produce normal blood cells. As a result, the bone marrow makes fewer and fewer healthy blood

cells. When the bone marrow is unable to make enough healthy white blood cells, a patient may also be more susceptible to infections. A decrease in the number of platelets can cause people to bleed and bruise easily. In order to make up for the low number of blood cells, other organs in the body, such as the spleen and liver, may begin to produce blood cells. This process of formation and development of blood cells outside the bone marrow is called "extramedullary hematopoiesis," and often causes the spleen and the liver to become enlarged.

In some people, MF gets worse over time. Approximately 9 to 13 percent of all cases transform into acute myeloid leukemia (AML), an aggressive form of blood cancer. However, some patients with MF live symptom-free for years.

Prognostic Scoring Systems. Certain factors can affect a patient's prognosis (a person's chance of recovery or the likely outcome of their disease). These are called "prognostic factors," and they help doctors predict how a patient's disease is likely to respond to treatment. These factors help doctors plan the most appropriate treatment for each patient. In addition, they may help determine whether allogeneic stem cell transplantation should be considered as a treatment option.

Prognostic scoring systems are used to evaluate treatment options for patients. There are multiple scoring systems available to help doctors predict the prognosis of patients with MF based on assessment of their risk factors. The four most common ones are the Dynamic International Prognostic Scoring System (DIPSS), the DIPSS Plus, the Mutation-Enhanced International Prognostic Scoring System 70 (MIPSS-70) and the MIPSS70-plus Version 2.0.

Researchers are beginning to incorporate information from biomarker testing results as a prognostic factor in patients with MF. The MIPSS70 incorporates the clinical characteristics of the patient's disease as well as specific chromosomal abnormalities and genetic mutations into a single system. For example, mutations in certain genes, such as *CALR,* are associated with better overall survival than others, like *JAK2* or *MPL*. The MIPSS70 is used to predict outcomes of patients aged 70 years and younger. It was recently reviewed and updated to incorporate additional cytogenetic information; the new version is the MIPSS70-plus Version 2.0.

The MIPSS70-Plus version 2.0 categorizes patients into four risk groups based on eight risk factors including age, blood counts, symptoms and genetic mutations. For each factor that a patient has, one point is assigned. The points are totaled to determine the score and corresponding risk group for the patient, as follows:

- 0 points = very low risk
- 1 to 2 points = low risk
- 3 to 4 points = intermediate risk
- 5 to 8 points = high risk
- 9 points or more = very high risk

You can find an MF-specific web calculator at https://pmfscorescalculator.com

Treatment Approach. The treatment approach for PMF is the same as it is for secondary MF (post-PV/ ET). However, there is no single treatment that is effective for all patients who have MF. Patients have varying symptoms and circumstances that require different treatment options. Some patients who have MF remain symptom-free for many years and do not require immediate treatment. All patients who have MF, however, need to be closely monitored.

Drug Therapies. There is no drug therapy that can cure MF. The only treatment that can potentially cure MF is allogeneic stem cell transplantation. But this procedure is risky for older patients and for those with other health problems. Because MF primarily affects older adults, stem cell transplantation is not a treatment option for most patients who have MF. Instead, treatment is focused on controlling disease symptoms and complications, enhancing quality of life and extending survival. Treatment decisions depend on the patient's risk category and symptom status.

Treatment for Patients Without Anemia. For patients **without anemia,** the treatment approach is based on the patient's prognostic level as well as the presence and severity of MF symptoms.

Lower Risk without Symptoms: Patients who are symptom-free and have no signs of anemia, an enlarged spleen or other complications at the time of diagnosis, are generally not treated. Some patients remain stable and symptom-free for many years. However, these patients still need to be monitored closely with regular medical checkups and tests to detect any signs and symptoms of disease progression. Treatment as part of a clinical trial is recommended if symptoms appear.

Lower Risk with Symptoms: The treatment approach for low-risk category patients who have symptoms of MF may be observation only. In certain circumstances, the doctor may prescribe cytoreductive treatment (a medication to lower blood cell counts) to help relieve the patient's symptoms. Treatment options include:

- Participation in a clinical trial
- Ruxolitinib (Jakafi®)
- Peginterferon alfa-2a (Pegasys®)
- Hydroxyurea (Hydrea®) to relieve symptoms caused by high blood counts
- Pacritinib (Vonjo®) if the platelet count is less than 50,000
- Momelotinib (Ojjaara)
- Fedratinib (Inrebic®)

Higher Risk and platelets are very low (below 50,000):

- Allogeneic stem cell transplant
- Participation in a clinical trial
- Pacritinib (Vonjo®) (preferred regimen) or momelotinib (Ojjaara)

Higher Risk and platelets are within the low to high range (50,000 or higher):

- Allogeneic stem cell transplant
- Participation in a clinical trial
- Ruxolitinib (Jakafi®), fedratinib (Inrebic®), momelotinib (Ojjaara), pacritinib (Vonjo®)

Treatments for Patients With Anemia. Most people with MF develop anemia within one year after diagnosis. For patients with anemia, the treatment approach depends on whether MF symptoms are present and, if present, on how well drug therapy is controlling these symptoms. Some of the recommended treatment options are listed below.

When there are no MF symptoms:

- Participation in a clinical trial
- Luspatercept-aamt (Reblozyl®)
- Erythropoiesis (EPO)-stimulating agents (ESA) if EPO level is lower than 500 mU/mL
- Momelotinib (Ojjaara)
- Pacritinib (Vonjo®)
- Receive red blood cell transfusions

When a JAK inhibitor drug is controlling MF symptoms:

- Participation in a clinical trial
- Luspatercept-aamt (Reblozyl®), erythropoiesis-stimulating agent (ESA) or ruxolitinib (Jakafi®)
- Switch current JAK inhibitor to either momelotinib (Ojjaara) or pacritinib (Vonjo®)
- Receive red blood cell transfusions

When MF symptoms are not controlled:

- Participation in a clinical trial

- Momelotinib (Ojjaara)
- Pacritinib (Vonjo®)
- Luspatercept-aamt (Reblozyl®), erythropoieses-stimulating agent (ESA) or ruxollitinib (Jakafi®)
- Receive red blood cell transfusions

See **Table 5** on page 42 and **Table 6** on page 43 for a list of medications used to treat MPNs, including MF.

Visit www.LLS.org/nutrition to receive nutrition education and to schedule a free consultation with a registered dietitian.

Allogeneic Stem Cell Transplantation. This is currently the only treatment that has the potential to cure MF – whether PMF or secondary MF (post-PV/ET). Allogeneic stem cell transplantation can induce remission and resolve bone marrow fibrosis, but it also carries a high risk of life-threatening side effects. It is a treatment option for patients with high-risk MF. It may also be an option for patients with low platelet counts or a complex karyotype.

In this procedure, the patient receives high doses of chemotherapy, either with or without radiation therapy, to kill the abnormal (cancerous) cells in the bone marrow. This part of the treatment, called "conditioning treatment," also kills healthy cells in the bone marrow. After the conditioning treatment is completed, patients receive an infusion of blood stem cells from a matched or partially matched donor. Blood stem cell donors may be either related or unrelated to the patient. The transplanted stem cells travel to the patient's bone marrow, repopulating the bone marrow space. The new cells grow and provide the patient with a new supply of red blood cells, white blood cells and platelets.

Allogeneic stem cell transplantation is associated with a higher rate of side effects and mortality than other treatments for MF. However, it may be considered as a treatment option for patients with higher-risk MF based on the genetic abnormalities of their cancer cells. The decision to perform an allogeneic transplant also depends on the patient's age and their understanding of the potential benefits and risks.

Allogeneic stem cell transplantation is a risky procedure for older patients and for those individuals with other health problems. It is therefore usually recommended only for younger patients with no other pre-existing health problems. However, allogeneic stem cell transplantation can be used in older people when considered medically appropriate. Whether or not a patient is a candidate for transplantation is determined by medical indications and the availability of a donor.

Reduced-intensity allogeneic stem cell transplantation may be a treatment option for older patients or patients with medical conditions who cannot tolerate the high doses of chemotherapy used in preparation for a standard allogeneic stem cell transplant. The conditioning therapy in a reduced-intensity transplant uses lower doses of chemotherapy. This therapy reduces the number of cancer cells, but it does not completely destroy all of the cancer cells. As in a standard allogeneic transplant, the immune cells (white blood cells) from the donor may recognize any remaining cancer cells as foreign and destroy them. This treatment may be safer than a traditional high-dose allogeneic transplant, especially for older patients. Patients should ask their doctors if stem cell transplantation is a treatment option for them. Even if a transplant is not needed immediately, it may be helpful to see a transplant specialist to get information and plan for any possible future transplant.

Visit www.LLS.org/booklets to view *Blood and Marrow Stem Cell Transplantation* and *Graft-Versus-Host Disease*.

Treatment Outcomes. Among patients with MF, the prognosis or likely outcome of the disease varies widely. Each patient's risk factors are evaluated individually to determine their prognosis. Some people with MF may survive for decades following their diagnosis.

It is important to know that outcome data can show how groups of people with an MPN responded to treatment in the past, but it cannot always determine how any particular person will respond. For these reasons, patients are advised to discuss information about survival with their doctors.

Supportive Care and Special Considerations

Supportive care is given to improve the quality of life for myeloproliferative neoplasm (MPN) patients and to prevent or treat the symptoms associated with these diseases.

See **Table 5** on page 42 and **Table 6** on page 43 for a list of medications used to treat MPNs.

Anemia. This is a condition in which the number of red blood cells is below normal. Anemia is observed in more than 50 percent of patients with MF at the time of diagnosis. Before considering treatment options, it is important for doctors to rule out and treat the most common causes of anemia, such as bleeding, iron deficiency and vitamin B12 and folic acid deficiency.

Blood transfusions are recommended for patients with anemia that is causing symptoms. Blood transfusions can increase a patient's red blood cell count and ease symptoms such as fatigue and weakness. Additional treatment options may be considered, based on the patient's serum erythropoietin (EPO) level.

Erythropoietin is a hormone needed for normal red blood cell production. In the body, it is made mainly by the kidneys.

Treatment recommendations for patients who have MF with anemia include:

- Darbepoetin alfa or epoetin alfa, which are drugs called "erythropoietin-stimulating agents (ESAs)." They are made in the laboratory and work by stimulating the bone marrow to make red blood cells.
- Danazol or other androgen drugs, which are synthetic versions of male hormones (androgens) that may help increase red blood cell production.
- The immunomodulators, thalidomide (Thalomid®) and lenalidomide (Revlimid®), are both given by mouth to help improve red blood cell counts. These drugs may be combined with prednisone, a steroid.
- Momelotinib (Ojjaara), a JAK inhibitor that can improve anemia as well as MF symptoms
- Luspatercept-aamt (Reblozyl®), an erythroid maturation agent that is currently under study in clinical trials.

Splenomegaly (Enlarged Spleen). Many patients with MPNs (polycythemia vera [PV], essential thrombocythemia [ET] or MF) have an enlarged spleen that may cause symptoms, such as abdominal discomfort, pain under the left ribs and a feeling of fullness without eating or after eating a small amount. There are several options for dealing with the painful effects of an enlarged spleen, including:

- Ruxolitinib (Jakafi®) and fedratinib (Inrebic®). These JAK inhibitors have been shown to reduce spleen size in some patients.
- Hydroxyurea (Hydrea®). This is a chemotherapy drug given by mouth that may reduce the size of an enlarged spleen and relieve related symptoms.
- Peginterferon alfa-2a (Pegasys®). This therapy can control an enlarged spleen.
- Splenectomy (surgical removal of the spleen). This may be considered if other forms of therapy have not reduced the pain, or complications associated with an enlarged spleen. However, the risks and benefits of this procedure need to be weighed.
- Radiation therapy. This treatment method uses high powered x-rays to shrink the spleen. When other treatment approaches have failed and surgical removal of the spleen is not a viable option, radiation therapy can be used to help reduce the size of the spleen.
- Embolization of the spleen. This minimally invasive treatment is an alternative to the surgical removal of all or part of the spleen. While the patient is sedated, the doctor injects embolizing agents through a catheter into an artery to block blood flow to the spleen in order to reduce its size.

Thrombocytosis and Leukocytosis. Some patients who have ET and MF suffer from thrombocytosis (in which the bone marrow produces too many platelets) or from leukocytosis (in which the bone marrow produces too many white blood cells). Hydroxyurea (Hydrea®) may be given to reduce the high platelet and white blood cell counts. It may also help treat other symptoms, including an enlarged spleen, night sweats and weight loss. Patients with low blood cell counts or severe anemia should not take hydroxyurea.

Surgery. If patients with MPNs require surgery, it is important to coordinate between your surgeon and your hematologist-oncologist and inform your surgeon that you have an increased risk for bleeding complications after surgery. For elective surgeries, it is recommended that your platelet and red blood counts be in normal range before the surgery occurs. If the surgery has a high risk for venous thrombosis, low molecular-weight heparin may be recommended. There should also be a plan to minimize the risk for deep vein thrombosis after surgery.

Aspirin use should be discontinued one week prior to an elective surgical procedure. After surgery, you will be monitored for bleeding and blood clots. You may start taking your medications again if the bleeding risk remains low. Aspirin may be restarted 24 hours after the surgery, or when considered acceptable by the treatment team depending on the level of bleeding risk.

Tumor Lysis Syndrome (TLS). As cancer cells break down and die, they release their contents into the bloodstream. Tumor lysis syndrome usually happens when chemotherapy is given and large amounts of cancer cells are destroyed. This can overwhelm the kidneys because they cannot get rid of these substances all at once.

Tumor lysis syndrome can be life threatening, but it can be prevented by administering high amounts of fluids during chemotherapy. Patients are constantly monitored for the development of TLS and are given drugs such as allopurinol (Zyloprim®) or rasburicase (Elitek®) to prevent or reduce the effects of this condition.

Pregnancy. Although people with MPNs are typically diagnosed in their 60s, sometimes younger people are diagnosed. If you are diagnosed with an MPN and are considering becoming pregnant, it is recommended that you meet with a high-risk obstetrician and speak to your hematologist-oncologist.

Nutrition and Cancer. Eating well is important for patients receiving treatment for blood cancer. Proper nutrition plays a key role in keeping the body strong, supporting the immune system and reducing the risk for diseases. Patients who eat well and maintain a healthy weight usually manage treatment and its side effects better. It is also important for patients with weakened immune systems to follow all food safety guidelines to reduce the risk of foodborne illness. Speak to your healthcare team about food and nutrition and for a referral to an oncology registered dietitian (RD) for specific nutrition advice and guidance.

Visit www.LLS.org/booklets to view *Food and Nutrition During Cancer Treatment* and *Nutrition Handbook: Feeding your family from meal planning to mealtime*.

LLS registered dietitians have expertise in oncology nutrition and provide patients, parents and caregivers with free nutrition consultations by phone. Visit www.LLS.org/nutrition or call 877-467-1936 to schedule a consult.

Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials, and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (U.S. Food and Drug Administration) requires all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug
  - Repurposing an approved drug to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug—by mouth (pill), intravenously (IV)
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist

oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes.

Clinical trials can be difficult to navigate and figure out, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find potential clinical trials, overcome barriers to enrollment and provide support throughout the entire clinical trial process. Our **Clinical Trial Nurse Navigators** are registered nurses who are experts in pediatric and adult blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (like past treatments, treatment responses, and your cancer genetic profile), your current health and your medical history—because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network and ability and willingness to travel might impact your choice of clinical trials
- Guide you and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical trial process

Call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers.*

Financial Concerns

Paying for healthcare is a major concern for many people who are living with a myeloproliferative neoplasm (MPN). The high cost of cancer treatment can lead to significant financial and emotional stress for both patients and their families. Even if you have health insurance, cancer can still take a toll on your finances. You may have new expenses such as co-payments or travel for treatment. You may also have less income if you need to take time off from work.

Speak with your healthcare team if you have any concerns about being able to afford your treatment. They may be able to provide information and resources that can help. Health insurance plans may not cover all of the costs of cancer care, but there are many resources available for prescription drug payment. In addition, several major drug manufacturers currently provide patient assistance or prescription assistance programs. These programs can provide both insured and uninsured patients free or reduced-cost medications.

LLS offers financial assistance programs to help with insurance premiums, treatment-related co-payments, travel and other expenses for eligible patients. Other organizations also offer financial assistance programs. You can call an LLS Information Specialist at (800) 955-4572 for more information about financial assistance programs.

For more information and resources to help cope with the financial costs of cancer care, please visit www.LLS.org/booklets to see the free LLS booklet *Cancer and Your Finances.*

Follow-Up Care and Survivorship

You will have frequent doctor appointments after you start treatment for a myeloproliferative neoplasm (MPN). Your doctor may recommend appointments every 3-6 months, or more frequently if complications occur. Blood tests will be done to monitor how well your treatment is working. If it appears your disease is progressing, a bone marrow aspiration and biopsy should be performed as clinically indicated. Your doctor will also monitor for new blood clots or bleeding and help you manage your cardiovascular risk factors.

After you complete treatment and are in remission, you will need to receive follow-up care. Patients should see a primary care doctor for a general health examination at least once a year and should also be examined regularly by an oncologist. Follow-up care involves regular medical check-ups. These check-ups may include blood work as well as other tests to look for signs of a relapse. The tests also check how well the patient's organs are working. This is important because MPNs and their treatments can damage organs.

During the first year, a patient will undergo frequent testing, but follow-up tests are given less often during the second and third years. As time goes on, a patient

may have less frequent testing and check-ups, but scheduled follow-up visits should continue indefinitely.

Each patient has a different follow-up care schedule. How often you have follow-up visits is based on the type of MPN you have, your overall health, and the treatments you have received. Your doctor will continue to monitor your symptoms. Using a tool such as the Myeloproliferative Neoplasm Assessment Form can help you discuss your symptoms with your doctor (see page 10).

Vaccines. Patients with MPNs are advised to receive certain vaccinations, including vaccinations for pneumococcal pneumonia and influenza, once they have finished their treatment. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Patients with MPNs should not be given vaccines that use live organisms or those with high viral loads, such as the herpes zoster (shingles) vaccine, but they can receive Shingrix because it is an inactivated shingles vaccine.

Current COVID-19 vaccines are also recommended. Patients with myelofibrosis (MF) on ruxolitinib may have an impaired immune response to the COVID-19 vaccination. Speak to your doctor for more information.

Survivorship. People who have been treated for an MPN are encouraged to:

- Maintain regular follow-up appointments with their hematologist-oncologist. The doctor will monitor them for signs of relapse and detect any side effects of treatment. A follow-up visit may also discover the onset of any other medical problems.
- Keep all records of their cancer diagnosis, treatments and follow-up care. This is often called a "survivorship care plan." Their doctor can provide a written survivorship care plan. This information can be shared with any new healthcare providers they see. The plan should include the following information:
  - List of all healthcare providers
  - Diagnosis summary with specifics such as subtype and/or genetic markers
  - Treatment summary with specifics such as the names, dates and dosages of chemotherapy or other drugs, site of radiation treatment, surgery and/or transplantation information, responses to treatment and side effects
  - Maintenance treatment information, if applicable
  - List of possible late effects
  - Schedule for ongoing monitoring with recommended tests, frequency of office visits/tests and coordinating provider(s)
  - Health and wellness recommendations such as nutrition and exercise, other disease screenings and vaccinations

- Receive periodic screening and monitoring for skin, gastrointestinal, kidney, blood, breast, lung, thyroid, head, neck and other types of cancer, because of the increased risk of a second cancer associated with MPNs.
- Seek medical and psychosocial support for fatigue, depression and other long-term effects, if needed.
- Consider cancer risk-reduction strategies, such as stopping smoking, protecting skin against prolonged sun exposure, healthy eating and exercising.

You may experience difficulties when you return to your daily routines after a long period of treatment. Getting support throughout this time, and for as long as needed, is important.

Visit www.LLS.org/SurvivorshipWorkbook to view or order the free survivorship workbook, *Navigating Life During and After a Blood Cancer Diagnosis,* with versions for adults, young adults and children and adolescents.

Drug Information

Table 5. Drug Classes and Drug Mechanisms

Anticoagulants	Anticoagulants decrease the clotting ability of the blood.
Antimetabolites	Chemotherapy drugs that interfere with the normal division and function of cancer cells. Antimetabolites mimic the building blocks of DNA or RNA that cancer cells need to survive and grow. When the cancer cell uses an antimetabolite instead of the natural substances, it cannot produce normal DNA or RNA and the cell dies.
Antiplatelet Agents	These drugs prevent platelets from sticking together and decrease the body's ability to form blood clots.
Erythroid Maturation Agents (EMAs)	Erythroid maturation agents help treat anemia by regulating the development of red blood cells. EMAs help erythroid cells (immature red blood cells) develop and become mature, functioning red blood cells.
Immunomodulators	Immunomodulatory drugs act in multiple ways to kill cancer cells and affect other cells, including immune system cells and structural cells. These drugs induce a cancer suppressor response directed by the immune system.
Janus Kinase (JAK) Inhibitors	These drugs block a protein called Janus kinase (JAK), which helps cells grow. JAK inhibitors block the action of this protein and stop the growth of cancer cells. They may also lower the body's immune response.
Platelet-reducing Agents	These drugs are used to decrease the number of platelets in the blood in order to prevent blood clotting.

Table 6. Some Drugs Used in the Treatment of Myeloproliferative Neoplasms

For more information, see the package insert and/or the full prescribing information for each medication (available on the internet). Some medications are dosed subcutaneously (sub-Q or SC) into the skin, others are dosed as an intravenous (IV) drip into a vein, and others are pills (oral).

Drug Name Administration Type of Drug	When the Drug is Commonly Used
Anagrelide hydrochloride (Agrylin®) Oral Platelet-reducing agent	Thrombocythemia, secondary MPNs
Aspirin Oral Antiplatelet Agent	• Low-or high-risk PV • ET
Fedratinib (Inrebic®) Oral JAK Inhibitor	Intermediate-2 or high-risk primary or secondary (post-PV or post-ET) MF
Hydroxyurea (Hydrea®) Oral Antimetabolite	• ET • PV
Low Molecular Weight Heparin (LMWH) Subcutaneous (SC) Anticoagulant	• PV • Pregnant patients who have PV with a history of venous thrombosis
Luspatercept-aamt (Reblozyl®) Subcutaneous (SC) Erythroid Maturation Agent (EMA)	Off-label treatment MF
Momelotinib (Ojjaara) Oral JAK Inhibitor	Intermediate or high-risk MF, including primary MF or secondary MF [post-PV and post-ET]
Pacritinib (Vonjo®) Oral JAK Inhibitor	Intermediate or high-risk primary or secondary (post-PV or post-ET) MF
Peginterferon alfa-2a (Pegasys®) Subcutaneous (SC) Immunomodulator	High-risk PV and ET ***Sometimes given to patients who are younger, pregnant or need to delay taking medications like hydroxyurea***

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; MF, myelofibrosis; PMF, primary myelofibrosis.

Table 6. Some Drugs Used in the Treatment of Myeloproliferative Neoplasms (con't)

Drug Name Administration Type of Drug	When the Drug is Commonly Used
Ruxolitinib (Jakafi®) Oral JAK Inhibitor	• Intermediate or high-risk MF, including PMF, secondary (post-PV or post-ET) MF • PV
Ropeginterferon alfa-2b-njft (Besremi®) Subcutaneous (SC) Immunomodulator	PV
Warfarin (Jantoven®) Oral Anticoagulant	Prevent and treat blood clots in patients who have PV and ET.

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; MF, myelofibrosis; PMF, primary myelofibrosis.

Incidence, Causes and Risk Factors

Incidence. Myeloproliferative neoplasms (MPNs) are relatively rare types of blood cancer. For the five-year period from 2015 and 2019, there were 67,181 new cases of MPNs throughout the US, averaging 13,436 cases per year. The overall age-adjusted incidence rate of MPNs is 3.5 cases per 100,000 population. An estimated 115,215 people in the US are living with or in remission from MPNs.

- Polycythemia vera (PV): The median age at diagnosis is 60 years. It is more common in males as compared to females.
- Essential thrombocythemia (ET): The median age at diagnosis is 60 to 70 years. It is more common in females.
- Myelofibrosis (MF): The median age at diagnosis is 67 years. It is slightly more common in males.

Risk Factors. A risk factor is anything that increases a person's chance of developing a disease. Myeloproliferative neoplasms are associated with genetic mutations (changes) that are somatic. This means the mutations are acquired during a person's lifetime rather than inherited. In some cases, MPNs have been found to run in families. However, people seem to inherit an increased risk of developing an MPN, not the disease itself.

Although the causes of the genetic mutations associated with MPNs are often unknown, certain factors increase a person's risk of developing an MPN. These risk factors include:

- **Age.** Myeloproliferative neoplasms are most commonly diagnosed in people 50 years and older. The risk of getting an MPN increases with age.

- **Prior MPN.** In a small number of patients, MF can develop from another type of MPN — either PV or ET.
- **Exposure to certain chemicals, such as benzene and toluene.** This has been linked to an increased risk of developing MF.
- **Exposure to radiation.** People exposed to very high levels of radiation, such as survivors of an atomic bomb blast or a nuclear reactor accident, have an increased risk of developing an MPN.

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals each have a special role. They include:

- Proteins
  - Albumin. This is the most common blood protein.
  - Blood-clotting proteins (coagulation factors). They are made by the liver.
  - Erythropoietin. It is made by the kidneys and stimulates red blood cell production.
  - Immunoglobulins. These are cells that fight infection.
- Hormones, such as thyroid hormones and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B-12
- Electrolytes, such as calcium, potassium and sodium

Blood Cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis" (see **Figure 2** on page 47). The blood cells are suspended in the plasma.

Once the blood cell is created, it will develop into one of the three types of blood cells.

These are:

1. Red blood cells are the cells that carry oxygen; they
   - Make up a little less than half of the body's total blood volume
   - Are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO_2 is removed from the lungs.

2. Platelets are cells that help blood clot; they
    - Are small cells (one-tenth the size of red blood cells)
    - Help stop bleeding from an injury or cut
    - Stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot, with the help of proteins, such as fibrin, and electrolytes, such as calcium.
3. White blood cells (WBCs) are cells that fight infections. The several types of WBCs include:
    - Neutrophils and monocytes. These are "phagocytes" (eating cells) that ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
    - Eosinophils and basophils. These WBCs respond to allergens or parasites.
    - Lymphocytes. WBCs found mostly in the lymph nodes, spleen and lymphatic channels, lymphocytes are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
        - T lymphocytes (T cells)
        - B lymphocytes (B cells)
        - Natural killer (NK cells)

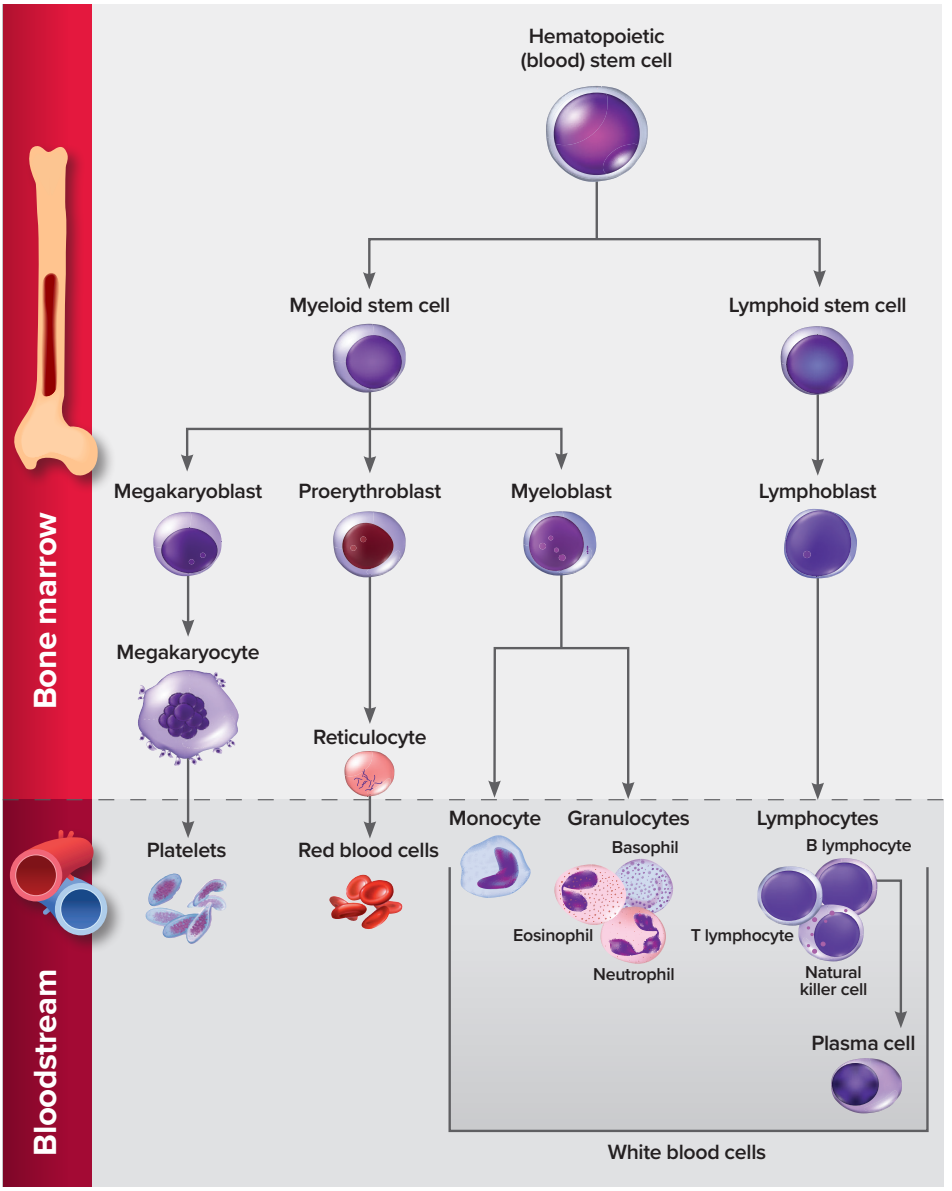
In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the bone marrow and then circulates throughout the body.

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, bone marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the bone marrow. These stem cells are important because they can be transplanted. Some stem cells enter the bloodstream and circulate; there are not enough of them to be counted in standard blood tests. Doctors know how to stimulate the growth of these cells in the bone marrow and have them migrate into the bloodstream. Then a special technique called "apheresis" is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be collected and stored for future use in transplantation.

Figure 2. Blood Cell and Lymphocyte Development

Most blood cells start as hematopoietic (blood) stem cells in the bone marrow. Hematopoietic stem cells are the most immature blood-forming cells. They must mature (go through many stages) to become a red blood cell, white blood cell or platelet. Some blood cells mature in the bone marrow. Other blood cells leave the bone marrow and travel to other parts of the body to develop into mature blood cells.



Additional Resources

Information for Firefighters. Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit www.LLS.org/FireFighters for resources and information.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam; to airborne hazards and burn pits while serving in Iraq, Afghanistan and other areas of Southwest Asia; to contaminated water at Camp Lejeune between 1953-1987; or to ionizing radiation during service may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: https://www.va.gov/disability/eligibility/hazardous-materials-exposure/

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Mental Health. Caring for your mental health has benefits for cancer patients. Seek medical advice if you are struggling. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov

If you or your loved one is experiencing a mental health crisis, call 988 to talk to a trained mental health professional. The 988 Suicide and Crisis Lifeline is free, confidential and always available. For the Crisis Text Line, text HOME to 741741.

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, visit www.LLS.org/ResourceDirectory to view the directory.

World Trade Center Health Program. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

Health Terms

Acute Myeloid Leukemia (AML). An aggressive, fast-growing type of blood cancer in which there are too many myeloblasts (immature white blood cells) in the blood and bone marrow.

Allogeneic Stem Cell Transplantation. A treatment that uses healthy donor stem cells to restore a patient's damaged or diseased bone marrow after receiving high doses of chemotherapy and/or radiation therapy. **See the free LLS booklet Blood and Marrow Stem Cell Transplantation.**

Anemia. A condition in which the number of red blood cells is below normal. This results in a diminished ability of the blood to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue, dizziness and shortness of breath.

Anticoagulant. A medication used to prevent and treat blood clots in blood vessels and the heart.

Artery. A blood vessel that carries blood from the heart to tissues and organs in the body.

Blast Cell. An immature blood cell.

Bone Marrow. Spongy tissue in the hollow central cavity of the bones where blood cells form.

Bone Marrow Aspiration. A procedure in which a liquid sample of bone marrow is removed for examination by a pathologist. After the patient is given a numbing agent, a sample is taken (usually from the patient's hip bone) using a special needle. Bone marrow aspiration and bone marrow biopsy are often done at the same visit and may be done in the doctor's office or in a hospital.

Bone Marrow Biopsy. A procedure in which a sample of bone with bone marrow is removed for examination by a pathologist. A sample is usually taken from the hip bone. After medication is given to numb the skin and tissue, a special hollow biopsy needle is used to remove a core of bone containing marrow. Bone marrow aspiration and bone marrow biopsy are often done at the same visit and may be done in the doctor's office or in a hospital.

Cardiovascular Risk Factors. Factors that raise a person's risk of coronary heart disease and heart attacks. These risk factors include family history, age, tobacco exposure, high blood pressure, high cholesterol, physical inactivity and diabetes.

Chemotherapy. Treatment that stops the growth of cancer cells, either by killing the cancer cells or by stopping them from dividing.

Chromosome. Part of a cell that contains genes in a linear order. Human cells have 23 pairs of chromosomes. **See the free LLS booklet Understanding Genetics.**

Chronic Myeloid Leukemia (CML). A slow-growing cancer in which there are too many myeloblasts (a type of white blood cell) in the blood and bone marrow. CML may get worse over time as the number of myeloblasts increases in the blood and bone marrow. **See the free LLS booklet Chronic Myeloid Leukemia for more information.**

Clinical Trial. A research study that is carefully planned and monitored to evaluate how well new medical approaches work in patients. The goal of clinical trials for blood cancers is to develop new treatments, improve quality of life and increase survival time. A treatment that is proven to be safe and effective in a clinical trial is often approved by the United States Food and Drug Administration (FDA) for use as a standard treatment for a disease, if it is either more effective or has fewer side effects than the current standard treatment for that disease.

Complex Karyotype. Three or more unrelated defects in chromosomes that occur in more than one cell.

Cytoreductive Therapy. Treatment that reduces the number of cells in the body. In patients with MPNs, cytoreductive therapy is prescribed to reduce the number of blood cells.

Deep Vein Thrombosis (DVT). The formation of a blood clot in a deep vein in the body, usually in the legs.

DNA. Abbreviation for deoxyribonucleic acid, the molecules found inside cells that carry genetic information. DNA is passed to new cells during the process of cell division. A change or mutation in the DNA can lead to cell death, changes in the cell function and, in some cases, cancer. **See the free LLS booklet Understanding Genetics.**

Embolism. A block in an artery caused by a blood clot or other substances. See Pulmonary Embolism.

Hematocrit. The percentage of whole blood that is made up of red blood cells.

Hematologist. A doctor who specializes in the treatment of blood diseases.

Hemoglobin. The iron-containing substance in red blood cells that carries oxygen around the body. Hemoglobin concentration decreases when there is a decrease in the number of red blood cells. This condition is called “anemia.”

Karyotype. An organized profile of a person’s chromosomes. It shows the size, shape and number of chromosomes in a sample of cells.

Mutation. A change in the DNA sequence of a cell. A mutation may be caused by a mistake in cell division, or it may be caused by contact with DNA-damaging substances in the environment.

Myelodysplastic Syndrome (MDS). A type of blood cancer in which the bone marrow does not make enough healthy blood cells. When there are fewer healthy blood cells, anemia, infection or bleeding may occur.

Off-Label Prescribing. Drugs that are not FDA-approved can be used as an "off-label" treatment. "Off-label" prescribing is when a doctor gives a drug that is not FDA-approved to treat a patient's condition, but is FDA-approved for another condition, if the doctor feels it will benefit the patient. This is a common practice.

Oncologist. A doctor who has special training in diagnosing and treating cancer.

Pathologist. A doctor who has special training in identifying diseases by studying tissue samples under a microscope.

Phlebotomy. A procedure in which a needle is used to take blood from a vein. It may also be done to remove extra red blood cells from the blood as part of the treatment for certain blood disorders.

Platelet. A small colorless blood cell fragment that helps control bleeding. Platelets travel to and then collect at the site of a wound. The platelets' sticky surfaces help them form clots at the site of the wound and stop bleeding. Also called "thrombocyte."

Prognosis. The probable outcome or expected course of a disease; the likelihood of recovery or recurrence of disease.

Pulmonary Embolism. A condition in which one or more arteries in the lungs become blocked by a blood clot.

Red Blood Cell. A type of blood cell that carries hemoglobin, which binds to oxygen and carries it to the tissues of the body. Red blood cells make up about 40-45 percent of the volume of blood in healthy individuals.

Risk Factor. Something that increases a person's chance of developing a disease. Risk factors can be genetic (inherited), lifestyle related or environmental.

Spleen. An organ in the left upper portion of the abdomen, just under the left side of the diaphragm. The spleen filters blood, stores blood cells and destroys old blood cells.

Stem Cell. An immature (undeveloped) cell that can develop into other cells. In the bone marrow, blood-forming stem cells mature into red blood cells, white blood cells and platelets. Stem cells can be collected, preserved and used for stem cell therapy.

Stroke. A loss of blood flow to part of the brain, which damages brain cells. Strokes are caused by blood clots and broken blood vessels in the brain. Symptoms of a stroke include dizziness, numbness and weakness on one side of the body, as well as problems talking, writing or understanding language.

Thrombocyte. See Platelet.

Thrombocythemia. A condition characterized by having too many platelets in the blood.

Thrombosis. The formation or presence of a blood clot (thrombus) inside a blood vessel.

Thrombus. A blood clot that forms and remains on the wall of a blood vessel or in the heart. It forms when platelets and other cells stick together. A thrombus may block the flow of blood in the blood vessel, depriving tissues of normal blood flow and oxygen.

Transfusion. A procedure in which whole blood or certain blood components are put into a patient's bloodstream.

Transient Ischemic Attack (TIA). A temporary blockage of blood flow to the brain. Symptoms of a TIA are like other stroke symptoms, but do not last as long.

Uric Acid. A waste product that is made and released into the blood when cells and other substances in the body break down. Most uric acid dissolves in blood and travels to the kidneys, where it is released in the urine. Abnormal buildup of uric acid in the body may cause "gout," a condition caused by increased levels of uric acid in the blood, joints and tissues. The buildup of uric acid causes inflammation and arthritis.

Vein. A blood vessel that carries blood to the heart from tissues and organs in the body.

White Blood Cell. A type of blood cell that is part of the body's immune system, which fights infection. There are five major types of white blood cells: neutrophils, eosinophils, basophils, monocytes and lymphocytes. See Normal Blood and Marrow on page 45.

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NOTES

A six-word narrative about living with blood cancer from patients in our LLS Community

Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/ happy I'm alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith and optimism. Finding joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.

Discover what thousands already have at **www.LLS.org/Community**

Join our online social network for people who are living with or supporting someone who has a blood cancer. Members will find:

- **Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff**
- **Accurate and cutting-edge disease updates**
- **The opportunity to participate in surveys that will help improve care**

LEUKEMIA & LYMPHOMA SOCIETY®

For more information, please contact our Information Specialists **800.955.4572** (Language interpreters available upon request.)

The Leukemia & Lymphoma Mail Center 1201 15th Street N.W., Suite 410 Washington, D.C. 2005

The mission of The Leukemia & Lymphoma Society (LLS) is to cure blood cancer and improve the quality of life of all patients and their families. Find out more at www.LLS.org.

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