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Myeloproliferative Neoplasms

Polycythemia Vera, Essential Thrombocythemia and Myelofibrosis

Revised **2021**

Support for this publication provided by Incyte

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, nutrition and optimism. Finding the 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.

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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**

Inside This Booklet

Acknowledgement

The Leukemia & Lymphoma Society (LLS) appreciates the review of this material by

Jeanne Palmer, MD
Program Director, Adult Bone Marrow Transplant
Hematology Section Head
Division of Hematology/Oncology, Department of Internal Medicine
Mayo Clinic
Phoenix, Arizona

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Introduction

Myeloproliferative neoplasms (MPNs) are a 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. MPNs 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.

We are here to help.

All LLS publications mentioned in this booklet are free and can be viewed, downloaded or ordered online at www.LLS.org/booklets.

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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

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.

This booklet provides information on the three classic types of MPNs that are traditionally grouped together because of their shared features. These include:

1. Polycythemia vera (PV)
2. Essential thrombocythemia (ET)
3. Myelofibrosis (MF)

Other types of MPNs include:

- Chronic myeloid leukemia (CML)
- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia (CEL)
- MPN unclassified (MPN-U)

These other types of MPNs are not covered in this booklet. 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.

How MPNs Develop. A mutation or a series of mutations 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 that proteins known as Janus kinases (JAKs) are involved. These proteins send signals 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 make JAKs, 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. MPNs 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, itchy skin, reddening of the face, 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."

Classic Types of MPNs. This booklet covers the three classic types of MPNs summarized below.

Polycythemia vera (PV): This MPN is characterized by the overproduction of red blood cells in the bone marrow. In many cases, the numbers of white blood cells and platelets also increase. These blood cells build up in the bone marrow and blood, causing the blood to thicken.

Essential thrombocythemia (ET): This MPN is characterized by the overproduction of platelets in the bone marrow. Platelets stick together and form blood clots to slow or stop bleeding and to help heal wounds. When there are too many platelets in the bloodstream, they may clump together and make it difficult for the blood to flow. High numbers of platelets may lead to a thrombus, a blood clot that forms in a blood vessel.

Myelofibrosis (MF): This MPN 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. As a result, the spleen and liver may begin to produce blood cells causing these organs to increase in size.

Vaccines. Patients with MPN 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 ShingrixR because it is an inactivated shingles vaccine. Current COVID-19 vaccines are also recommended, although they have not been specifically tested in patients with MPNs as of this printing. Speak to your doctor for more information.

Polycythemia Vera

Polycythemia vera (PV) is a rare type of blood cancer characterized by the overproduction of red blood cells. 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. But with careful medical supervision, it can usually be managed effectively for many years. In a small number of patients, PV may progress to a more aggressive type of blood cancer such as myelofibrosis (MF), myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

How PV Develops. Blood cells form in the bone marrow, where they begin as immature 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.

While the cause of PV is not fully understood, researchers believe that it begins with a mutation or series of mutations in the DNA (genetic material) of a blood stem cell. PV is associated with mutations in the *JAK2* gene, although other mutations may play a role as well.

The *JAK2* gene provides instructions for making a protein called "JAK2," which sends signals that promote the growth and division of cells. This protein helps control the number of red blood cells, white blood cells and platelets in the bone marrow. When the *JAK2* gene is mutated, this results in an activated JAK2 protein that seems to increase production of blood cells and prolongs their survival. This results in the buildup of too many blood cells in the body. Approximately 95 percent of PV patients have a mutation of the *JAK2* gene.

The mutation can also lead to the overproduction of cytokines. Cytokines are proteins released by cells that direct the immune system to fight invaders. They are crucial in controlling the growth and activity of immune system cells and blood cells, and some are associated with inflammation. Many patients with MPNs experience symptoms caused by inflammation. Symptoms of inflammation may include unexplained fevers, night sweats, itchy skin, reddening of the face and bone pain.

Signs and Symptoms

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

Patients with signs and/or symptoms of PV are referred to a hematologist-oncologist. A hematologist is a doctor who has special training in blood disorders, and an oncologist is a doctor who has special training in cancer. A hematologist-oncologist specializes in diagnosing and treating blood cancers.

PV 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.

Signs and symptoms of PV may include:

- Fatigue (tiredness)
- Pruritus (itchy skin) especially after warm baths or showers
- Reddened face and burning feeling on the skin
- Headaches, dizziness and weakness
- Difficulties concentrating
- Night sweats
- Insomnia
- Blurred vision, double vision, or seeing dark or blind spots that come and go
- 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 small amounts of food
- Weight loss for no known reason
- Bone pain

When PV causes symptoms, they can be troublesome. Reducing symptoms is a key goal of treatment. Therefore, it is important to take an active role in monitoring your PV 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 that you and your doctor can use to evaluate your symptoms is the Myeloproliferative Neoplasm Symptom Assessment Form (see **Table 1** on page 8). 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 PV be assessed both before and during treatment. Worsening symptoms can be a sign of disease progression and should be reported promptly to the doctor.

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: MPD, myeloproliferative disorder.

Adapted from Emanuel RM, et al. *Journal of Clinical Oncology*. 2012. National Comprehensive Cancer Network (NCCN). Guidelines for Physicians. *Myeloproliferative Neoplasms.* 2021. (Please see References.)

Complications

In medicine, a complication is a medical problem that occurs during the course of a disease or after a procedure or treatment. Possible complications of PV include:

- **Thrombus (blood clot).** The extra blood cells in people with PV may cause the blood to be thicker than normal. As a result, harmful blood clots may form and block the flow of blood through arteries and veins. Blood clots that form in an artery can lead to a heart attack or a stroke. They can also form in the deep veins of the arms or legs, a condition called "deep vein thrombosis." If a blood clot from a deep vein breaks loose and travels to the lungs, it can become lodged in the lungs, blocking blood flow, which can be life-threatening. This is called a "pulmonary embolism."
- **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. In some people with PV, the spleen may become abnormally enlarged 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.
- **Other blood diseases.** In some cases, PV may progress to other related blood diseases including myelofibrosis (MF), acute myeloid leukemia (AML) and, less commonly, myelodysplastic syndrome (MDS).

Diagnostic Tests

While certain signs and symptoms may indicate that a person has PV, 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

Some of these tests may be repeated both during and after treatment to evaluate whether treatment is effective.

Medical History and Physical Examination. If a person has signs or symptoms of PV, 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 and other treatments
- 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

After completing the medical history, the doctor will conduct a physical examination. During the exam, the doctor may listen to your lungs and heart and carefully examine your body for signs of infection and disease. To check your internal organs, the doctor may feel different parts of your body. 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 measures the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin, the iron-rich protein that carries oxygen in red blood cells, and the hematocrit, the percent 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 PV have high red blood cell counts. They also often have:

- Increased hemoglobin levels
- Increased hematocrit levels
- Increased white blood cell and platelet counts

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 newer blood tests that can be used to diagnose PV, such as molecular tests (see page 13).

Blood Chemistry Profile. This blood test measures 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 PV, if the results show that there is an abnormal

amount of a particular substance in the blood, it may be a sign of disease or some other health problem.

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. These are two procedures that 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 (aspirate) 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 12 for more information on blood and bone marrow tests.

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. People with PV have above-normal numbers of blood cells, as well as an abnormal number of megakaryocytes (platelet-forming cells) in the bone marrow.

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.

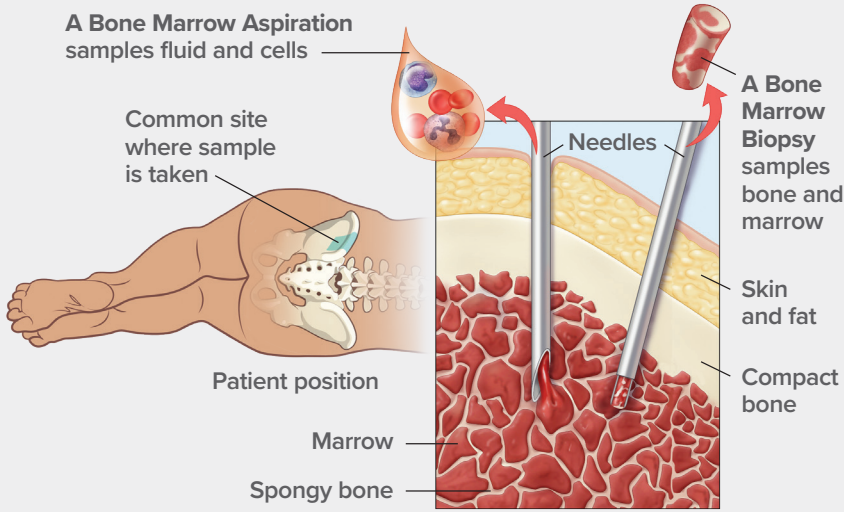
Bone Marrow Aspiration. A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

Bone Marrow Biopsy. A very small amount of bone filled with bone 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 procedue. They get medication first to numb the part of the body that will be used to get the sample of cells. Some patients are given a drug that makes them "sleep" during this procedure. 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. A 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 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.

Molecular Tests. These tests look for abnormal changes in the genes, chromosomes, proteins or other molecules within the patient's cancer cells. They are used for diagnosis and treatment planning.

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 that 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.

DNA sequencing: DNA sequencing refers to a number of different laboratory tests that examine the exact sequence (order) of DNA. By comparing the sequence of DNA in cancer cells with the DNA in normal cells, doctors can find genetic changes that are unique to the cancer cells and may be driving the growth of the patient's cancer. DNA sequencing can be done with blood or bone marrow samples.

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 PV patients. If a patient does not have a *JAK2 V617F* mutation, then testing should be done for other mutations. About 2-3 percent of PV patients have the *JAK2* exon 12 mutation.

See the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics* for more information about these tests. To view interactive, 3D illustrations of certain lab and imaging tests, visit www.LLS.org/3D.

Diagnosis

In 2016, the World Health Organization published criteria for diagnosing PV. These criteria are summarized in **Table 2** on page 14. For a diagnosis of PV to be made, all three of the "major criteria" must be met (Major Criteria 1, 2, and 3), or the first two major criteria (Major Criteria 1 and 2) and the minor criterion.

Table. 2 World Health Organization Diagnostic Criteria for 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 men • Hemoglobin level greater than 16.0 g/dL in women OR B. Elevated hematocrit level • Hematocrit greater than 49 percent in men • Hematocrit greater than 48 percent in women 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

Treatment Options

New treatments may have been approved since this book 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 of 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. PV is part of a group of rare similar blood cancers called "myeloproliferative neoplasms (MPNs)." So it is important to seek

treatment in a center with hematologist-oncologists who have experience in the care of patients with MPNs.

See the free LLS publication *Choosing a Blood Cancer Specialist* or *Treatment Center* for more information.

Risk Factors. PV is a chronic disease. It is not curable, but it usually can be managed effectively for very long periods. 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.

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:

- History of thrombosis (a previous blood clot)
- Advanced age (60 years or older)

Low risk: PV patients who are younger than 60 years with no history of thrombosis.

High risk: PV patients who are 60 years or older and/or have a history of thrombosis.

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 men, or 42 percent for women. Careful medical supervision and therapy is important to keep the hematocrit at a normal level. See **Table 3** below for an overview of initial treatments for PV based on the patient's risk profile.

Table 3. Initial Treatment for Polycythemia Vera

Risk Groups	
Low Risk	• Monitor for new clots or bleeding • Manage cardiovascular risk factors • Low-dose aspirin (80-100 mg per day) • Phlebotomy (to keep hematocrit below 45 percent for men, or 42 percent for women)
High risk	• Monitor for new clots or bleeding • Manage cardiovascular risk factors • Low-dose aspirin (80-100 mg per day) • Phlebotomy (to keep hematocrit below 45 percent for men, or 42 percent for women) • Cytoreductive therapy (medications to reduce the number of blood cells)

Adapted from National Comprehensive Cancer Center (NCCN) Clinical Practice Guidelines. *Myeloproliferative Neoplasms*. 2021. (Please see References.)

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 PV patients 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.

Cytoreductive Therapy (Medications to Reduce the Number of Blood Cells). High-risk category PV patients 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®).** This chemotherapy drug is taken by mouth as a pill or capsule. Although it is not approved by the Food and Drug Administration (FDA) for the treatment of PV, it is the most commonly prescribed drug for PV to help reduce the number of blood cells made in the bone marrow and to reduce an enlarged spleen. It is used for high-risk category patients who cannot tolerate frequent phlebotomy treatments, and for patients with high blood counts and enlarged spleens. Common side effects include low white blood cell count (which increases the risk of infection), low platelet counts (which increase the risk of bleeding), nausea, vomiting, diarrhea, and ulcers in the mouth.
- **Ruxolitinib (Jakafi®).** This drug is a JAK1/JAK2 inhibitor taken by mouth. It is approved by the FDA as a second-line therapy in adults who have had an inadequate response to or are intolerant of hydroxyurea. JAK proteins send signals that affect the production of blood cells in the bone marrow. When JAKs send too many signals, it causes the body to make too many blood cells. Ruxolitinib works by inhibiting the JAK proteins and reducing the overactive signaling. The most common side effects include low blood cell counts, bruising, dizziness, headaches, infections and diarrhea.
- **Interferon alfa-2b (Intron® A) and interferon alfa-2a (Roferon®-A) and their associated sustained-release preparations, peginterferon alfa-2b (PEG-Intron®) and peginterferon alfa-2a (Pegasys®).** Interferon is a biological agent used to stimulate the immune system to fight the overproduction of red blood cells. It may be used for patients who are either intolerant or resistant to hydroxyurea, or for patients for whom hydroxyurea is not recommended.

Interferon is not used for most patients. This is because, compared to other treatment options for PV, it is less convenient to administer (because it is given by intramuscular or subcutaneous injection) and may cause troublesome side effects. Some patients experience moderately severe flu-like symptoms, confusion, depression or other complications.

- **Busulfan (Myleran®).** This is a chemotherapy drug taken by mouth to help lower blood cell counts. It may be prescribed for patients with PV who cannot tolerate other medications. It is usually prescribed when other therapies for PV have not been effective or are not tolerated well, especially in older patients. Common side effects include low blood cell counts, nausea and vomiting, diarrhea, poor appetite and mouth sores.

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). Low-molecular-weight heparin is a class of blood thinner medications that are injected through the skin at home. Another option is an oral blood thinner, taken by mouth, such as warfarin, apixaban or rivaroxaban. 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 that 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.

Treatments to Reduce Itching. A troublesome symptom that occurs in many PV patients 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 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, 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®)** or **doxepin**, which may help with itching that does not go away. Side effects of antihistamines include dry mouth, drowsiness, dizziness and restlessness.
- 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 Monitoring

You will have frequent doctor appointments after you start treatment for PV. 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 that your disease is progressing, a bone marrow aspiration and biopsy should be performed as clinically indicated.

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 8). Your doctor will also monitor for new blood clots or bleeding and help you manage your cardiovascular risk factors.

Special Considerations

Surgery. Patients with PV have increased risk for bleeding complications after surgery. Because your surgeon may not be aware of your increased risk for bleeding and blood clots, coordination between your surgeon and your hematologist-oncologist is very important. For elective surgeries, it is recommended that your platelet and red blood counts be in normal range before the surgery occurs. Aspirin use should be discontinued one week prior to an elective surgical procedure and then restarted 24 hours after the surgery, or when considered acceptable depending on the level of bleeding risk. Anticoagulant therapy should likewise be suspended prior to surgery and restarted after surgery, again when considered acceptable depending on bleeding risk. There should also be a plan to minimize the risk for deep vein thrombosis after surgery.

Pregnancy. Although MPNs typically develop later in adulthood, some people younger than age 40 are diagnosed with PV. Pregnancies are considered high-risk in younger women with PV. If you have PV and are considering a pregnancy, it is recommended that you meet with an obstetrician specializing in high-risk pregnancies before you become pregnant. Your doctor may recommend taking aspirin during and shortly after your pregnancy. Sometimes, use of an injectable anticoagulant called "**enoxaparin (Lovenox®)**" is recommended for 6 weeks following the delivery of the child. Hydroxyurea should not be taken during pregnancy or while breastfeeding, as it may harm your baby. If you are taking hydroxyurea, you may switch to interferon during your pregnancy.

Research and Clinical Trials

New treatment approaches for PV are under study in clinical trials, many of which are supported by LLS research programs.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of the standard treatment for a disease. Clinical trials are carefully designed and reviewed by expert clinicians and researchers as well as patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time you discuss treatment with your doctor. Patient participation in past clinical trials has resulted in the FDA-approved therapies we have today.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option for them. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and their caregivers can work with Clinical Trial Nurse Navigators who will help

find clinical trials and personally assist them throughout the entire clinical trial process. Visit the LLS Clinical Trial Support Center webpage at www.LLS.org/CTSC for more information.

Research Approaches. There are clinical trials for newly diagnosed patients, for patients with advanced disease, and for patients who are intolerant of or resistant to their current medications. Researchers are currently studying:

- Gene mutations and cellular pathways involved in the development of PV to help develop new drugs to target PV
- New treatments to reduce the risk of thrombosis and cardiovascular complications and to improve quality of life for PV patients
- New therapies to prevent PV from progressing to more serious blood diseases
- New treatments to help high-risk PV patients live a normal life span

Some drugs under investigation include:

- **Ropeginterferon alfa-2b.** In the past, the use of interferon was restricted because it was not well tolerated by patients. However, there is a good deal of interest in interferon's ability to induce a molecular response (remission) in some patients. This type of treatment response occurs in patients with PV when there is a decrease in the number of cells with the abnormal *JAK2* gene mutation. New formulations of interferon may be effective in achieving a molecular remission with fewer side effects and less frequent doses. Researchers are evaluating "pegylated" formulations of interferon that can be given less often, since they remain in the body longer. High molecular response rates have been demonstrated in studies. In 2019, ropeginterferon alfa-2b was approved by the European Medicines Agency for the treatment of polycythemia vera in patients without symptoms of an enlarged spleen. It is now being studied in clinical trials in the United States.
- **Histone deacetylase inhibitors (HDAC).** HDAC inhibitors are substances that cause chemical changes that stop abnormal cells from growing or dividing. They show promise as "salvage therapies," which are given when first-line treatment options fail. Researchers are studying whether **givinostat** is an effective second-line treatment for patients who are intolerant or refractory to hydroxyurea. Researchers are also evaluating the use of givinostat in combination with low-dose hydroxyurea.
- **JAK Inhibitors.** The FDA-approved drug **ruxolitinib (Jakafi®)** is being studied for use in patients with PV who have had an inadequate response to or are intolerant of hydroxyurea. It is also being evaluated in combination with other drugs, including pegylated interferon, for PV treatment.

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.

Incidence, Causes and Risk Factors

PV is a rare blood cancer. In the United States, the age-adjusted incidence rate of PV was approximately 1.3 people per 100,000 persons in 2013-2017. It affects slightly more males than females. While PV can occur at any age, it occurs most often in individuals who are older than age 60.

PV is associated with genetic mutations (changes) that are somatic. Mutations that are “somatic” are not inherited, but rather are acquired during a person’s lifetime. At this time, the exact causes of these mutations are unknown. In rare cases, PV has been found to run in families. However, people seem to inherit an increased risk of developing PV, not the disease itself.

Essential Thrombocythemia

Essential thrombocythemia (ET) is a rare type of blood cancer characterized by the overproduction of thrombocytes (platelets). The word "thrombocythemia" means a disease in which the bone marrow makes too many platelets. ET is sometimes also called "primary thrombocythemia," "idiopathic thrombocythemia" or "primary thrombocytosis."

Platelets are pieces or fragments of large cells in the bone marrow called "megakaryocytes." Normally, pieces of a megakaryocyte break off and enter the bloodstream as platelets. In the bloodstream, platelets travel throughout the body and stick together to form blood clots to slow or stop bleeding and to help heal wounds. But when there are too many platelets in the bloodstream, they may clump together and make it difficult for the blood to flow. High numbers of platelets may lead to a thrombus, a blood clot that forms in a blood vessel. 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.

How ET Develops. Blood cells form in the bone marrow, where they begin as immature, undeveloped 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.

While the cause of ET is not fully understood, researchers believe that it begins with a mutation or series of mutations in the DNA (genetic material) of a blood stem cell in the bone marrow. This results in the overproduction of megakaryocytes, the cells that form platelets in the bone marrow.

The majority 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. Mutation of these genes increases the production megakaryocytes, which in turn results in an increased number of platelets.

About 10 percent of ET patients do not have a *JAK2*, *MPL* or *CALR* gene mutation. In these cases, the disease is referred to as "triple-negative" ET. Further study is needed to identify other mutations that may cause the disease in these patients.

Signs and Symptoms

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

Patients with signs or symptoms of ET are referred to a hematologist-oncologist. A hematologist is a doctor who has special training in blood disorders, and an oncologist is a doctor who has special training in cancer. A hematologist-oncologist specializes in diagnosing and treating blood cancers.

ET 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. The signs and symptoms of ET are linked to high platelet counts that 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
- Weight loss
- Low-grade fevers
- Night sweats

- Pain, redness and swelling in the hands or feet (called “erythromelalgia”), caused by diminished blood flow
- Enlarged spleen

Symptoms of ET can be troublesome. Reducing symptoms is a key goal of treatment. Therefore, it is important to take an active role in monitoring your ET 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 that you can use to evaluate your symptoms is the Myeloproliferative Neoplasm Symptom Assessment Form (see **Table 4** on page 25). 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 ET be assessed both before and during treatment. Worsening symptoms can be a sign of disease progression and should be reported promptly to the doctor.

Complications

In medicine, a complication is a medical problem that occurs during the course of a disease or after a procedure or treatment. Possible complications of ET include:

- **Deep vein thrombosis.** 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.** If a blood clot occurs in the arteries that supply blood to the brain, it may cause a stroke or a transient ischemic attack (TIA). A stroke is a loss of blood flow to part of the brain, which damages brain tissue. A TIA is a type of stroke that only last a few minutes when the blood supply to part of the brain is briefly blocked.
- **Heart attack.** If a clot blocks blood flow to the heart, it can cause a heart attack. Without blood, tissue in the heart 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.
- **Other blood diseases.** In some cases, ET patients can develop myelofibrosis, another type of MPN that results in bone scarring, anemia and enlargement of the spleen and liver. In a smaller number of cases, ET may transform into a myelodysplastic syndrome or acute myeloid leukemia.

Table 4. 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: MPD, myeloproliferative disorder.

Adapted from Emanuel RM, et al. *Journal of Clinical Oncology*. 2012. National Comprehensive Cancer Network (NCCN). Guidelines for Physicians. *Myeloproliferative Neoplasms.* 2021. (Please see References.)

Diagnostic Tests

While certain signs and symptoms may indicate that a person has ET, 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

Some of these tests may be repeated both during and after treatment to evaluate its effectiveness.

Medical History and Physical Examination. If a person has signs or symptoms of ET, 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 and other treatments
- History of a thrombus (blood clot) or hemorrhagic events (loss of blood from damaged blood vessels)
- Medical history of blood relatives because some illnesses run in families
- Current symptoms

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

Complete Blood Count with Differential. This test measures the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin, the iron-rich protein that carries oxygen in red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample. In patients with ET, the platelet count is higher than 450 x 10^9/L (a normal platelet count ranges from 150 x 10^9/L to 450 x 10^9/L).

Peripheral Blood Smear. In this procedure, a sample of blood is viewed under a microscope to see 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.

Blood Chemistry Profile. This blood test measures 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 ET, if the results show that there is an abnormal amount of a particular substance in the blood, it may be a sign of disease or some other health problem.

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.

Bone Marrow Aspiration and Biopsy. These are two procedures that 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, 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 (aspirate) 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 2** on page 28 for more information on blood and bone marrow tests.

The samples are 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. 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.

Figure 2. 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.

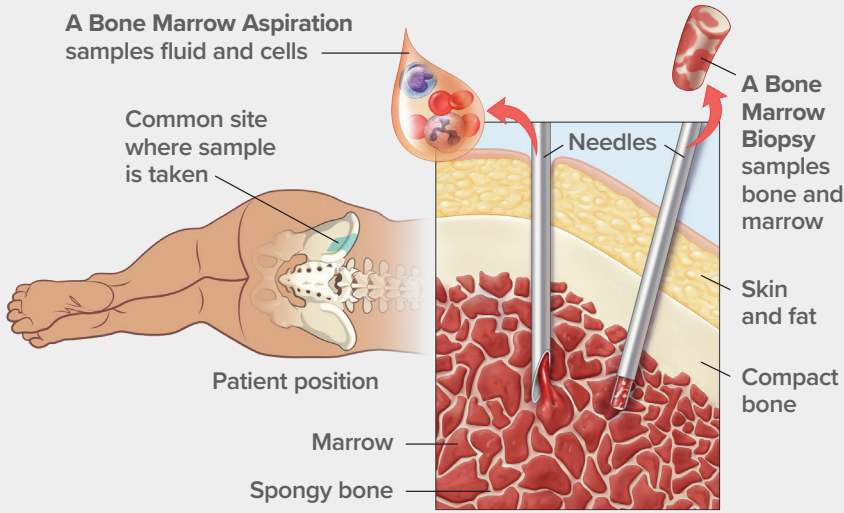
Bone Marrow Aspiration. A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

Bone Marrow Biopsy. A very small amount of bone filled with bone 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 procedue. They get medication first to numb the part of the body that will be used to get the sample of cells. Some patients are given a drug that makes them "sleep" during this procedure. 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. A 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 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.

Molecular Tests. These tests look for abnormal changes in the genes, chromosomes, proteins or other molecules within the patient's cancer cells. They are used for diagnosis and treatment planning.

Polymerase chain reaction (PCR). This is a very sensitive test that is used to detect and measure specific genetic mutations that are too small to be seen with a microscope. PCR testing essentially amplifies (increases) small amounts of specific pieces of DNA so that 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.

DNA sequencing. This term refers to a number of different laboratory tests that examine the exact sequence (order) of DNA. By comparing the sequence of DNA in cancer cells with the DNA in normal cells, doctors can find genetic changes that are unique to the cancer cells and may be driving growth of the patient's cancer. DNA sequencing can be done with blood or bone marrow samples.

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 — 60%
- *CALR* mutation — 20%-35%
- *MPL* mutation — 1%-4%

About 10 percent of ET patients do not have a *JAK2*, *MPL* or *CALR* gene mutation. In these cases, the disease is referred to as "triple-negative" ET. Further study is needed to identify other mutations that may cause the disease in these patients.

See the free LLS booklet *Understanding Lab and Imaging Tests* and *Understanding Genetics* for more information about these tests. To view interactive, 3D illustrations of certain lab and imaging tests, visit www.LLS.org/3D.

Diagnosis

In 2016, the World Health Organization (WHO) published new criteria for diagnosing ET. These criteria are summarized in **Table 5** on page 30. For a diagnosis of ET to be made, all four of the major criteria must be met or, major criteria 1-3 plus minor criterion must be met.

Table 5. World Health Organization Diagnostic Criteria for ET

Essential Thrombocythemia Diagnosis requires 4 major criteria OR major criteria 1-3 + 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
Minor Criterion
Presence of a clonal marker (chromosome abnormality), **or** no evidence that the disorder is caused by reactive thrombocytosis

Treatment Options

New treatments may have been approved since this book 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. ET is part of a group of rare similar blood cancers called "myeloproliferative neoplasms (MPNs)." So it is important to seek treatment in a center with hematologist-oncologists who have experience in the care of patients with MPNs.

See the free LLS publication *Choosing a Blood Cancer Specialist* or *Treatment Center* for more information.

Risk Factors. Decisions about treatment for ET are based on the patient's risk for developing blood clots. The International Prognostic Score for ET (IPSET) groups patients into four risk categories: very low risk, low risk, intermediate risk and high risk.

Risk Category	Patient Characteristics	Treatment Approach
Very low	Age 60 years or younger, no history of thrombosis, no *JAK2* gene mutation	Observation only
Low	Age 60 years or younger, no history of thrombosis, *JAK2* gene mutation	Low-dose aspirin
Intermediate	Older than 60 years, no history of thrombosis no *JAK2* mutation	Low-dose aspirin with or without cytoreductive therapy
High	Older than 60 years, history of thrombosis, *JAK2* mutation	Low-dose aspirin with cytoreductive therapy

Any patient who develops a venous blood clot requires lifelong treatment with anticoagulants.

The main objective of treatment for ET is the prevention of thrombosis (formation of blood clots). Your hematologist-oncologist can recommend specific treatments to manage your ET. 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.

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

Very low risk: For patients who have no cardiovascular risk factors, the disease is considered to be low risk and may be managed with observation alone. No drugs are given at this time, but regular exams and blood tests are done to determine whether the disease is stable or beginning to progress. The doctor will also monitor very low-risk patients for the formation of new blood clots.

Low risk: Patients in this category are considered to have a low risk of complications. The doctor may prescribe low-dose aspirin and help manage any cardiovascular risk factors, such as high blood pressure and diabetes. Regular exams and blood tests are done to watch for any signs of disease progression. The doctor will also monitor low-risk patients for the formation of new blood clots.

Intermediate risk: For patients in the intermediate-risk category who have no symptoms, the doctor may prescribe low-dose aspirin, either with or without cytoreductive therapy, and help manage any cardiovascular risk factors, such as high blood pressure and diabetes. Regular exams and blood tests are done to watch for any signs of disease progression. The doctor will also monitor intermediate-risk patients for the formation of new blood clots.

High risk: For patients in the high-risk category, the doctor may prescribe low-dose aspirin to prevent thrombosis in combination with cytoreductive therapy to reduce high platelet counts. Regular exams and blood tests are done to watch for any signs of disease progression. The doctor will also monitor high-risk patients for the formation of new blood clots.

Drug Therapy. The treatment of ET may include:

Low-Dose Aspirin (80-100 mg per day). Taking low-dose aspirin daily may reduce the risk of clotting complications. It also helps prevent platelets from sticking together, making it less likely for blood clots to form, which can cause heart attacks or strokes. The most common side effects of aspirin include upset stomach and heartburn. Low-dose aspirin may also increase bleeding risk in patients with extremely high platelet counts. For these reasons, the use of aspirin in treating ET needs to be individualized, based on each patient's situation.

Cytoreductive Therapy. This refers to a group of medications that reduce the number of blood cells in the bone marrow. The goal is to reduce the platelet count to below 450 x 10^9/L.

- **Hydroxyurea (Hydrea®).** This chemotherapy drug is taken by mouth as a pill or capsule. It is prescribed to help decrease the number of blood cells made in the bone marrow. Although it is not approved by the Food and Drug Administration (FDA) for the treatment of ET, it is the drug prescribed most frequently as a first-line therapy for patients with ET. Hydroxyurea is often successful in decreasing the platelet count within several weeks, and the side effects are minimal and short-term. Common side effects include low white blood cell count (which increases the risk of infection), nausea, vomiting, diarrhea and ulcers in the mouth.
- **Anagrelide (Agrylin®).** This drug is FDA approved to reduce an elevated platelet count in patients with ET. It is taken by mouth as a capsule. Headaches are a common side effect. Less common side effects include heart palpitations, nausea, diarrhea and dizziness. A rare but serious side effect can be interference with the pumping action of the heart or even a heart attack.
- **Interferon alfa-2b (Intron® A) and interferon alfa-2a (Roferon®-A) and their associated sustained-release preparations, peginterferon alfa-2b (PEG-Intron®) and peginterferon alfa-2a (Pegasys®).** Interferon is another treatment option for lowering platelet counts in patients with ET. It may be

used for patients who are either intolerant or resistant to hydroxyurea, or for younger patients for whom hydroxyurea is not recommended. However, it is not used in most patients. This is because, compared to other treatments for ET, it is less convenient to administer (it is given by injection) and may cause troublesome side effects. Some patients experience moderately severe flu-like symptoms, confusion, depression or other complications.

- **Busulfan (Myleran®).** This is a chemotherapy drug taken by mouth to lower blood cell counts. It is used as a second-line treatment in older patients who are resistant or intolerant to hydroxyurea. Common side effects include low blood counts, nausea and vomiting, diarrhea, poor appetite and mouth sores.

Plateletpheresis. 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 can be safely self-injected by the patient at home. Another option is an oral blood thinner, taken by mouth, such as warfarin, apixaban or rivaroxaban. For life-threatening blood clots that have already formed, drugs called "thrombolytics" can be given to dissolve them.

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 or control it.
- **Keeping your cholesterol under control.** A high cholesterol level in the blood can clog arteries and raise your risk 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 narrow 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.

Treatment Monitoring

You will have frequent doctor appointments after you start treatment for ET. 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 that your symptoms are increasing and the disease is progressing, a bone marrow aspiration and biopsy should be performed as clinically indicated.

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 25). Your doctor will also monitor for new blood clots or bleeding and help you manage your cardiovascular risk factors.

Special Considerations

Surgery. Patients with ET have increased risk for bleeding complications after surgery. Because your surgeon may not be aware of your increased risks of bleeding and blood clots, coordination between your surgeon and your hematologist-oncologist is very important. For elective surgeries, it is recommended that your platelet counts be in a normal range before the surgery occurs. Aspirin use should be discontinued one week prior to an elective surgical procedure and then restarted 24 hours after the surgery, or when considered acceptable depending on the level of bleeding risk. Anticoagulant therapy should likewise be discontinued prior to surgery and restarted after surgery, again when considered acceptable depending on the bleeding risk. There should also be a plan to minimize the risk for excessive bleeding and deep vein

thrombosis (DVT) after surgery.

Pregnancy. In general, pregnancy increases a woman's risk of blood clots, and pregnant women with ET are particularly susceptible to them. Due to the risks to the developing fetus, many medications used to treat ET should be avoided during pregnancy, including hydroxyurea and anagrelide. Treatment with low-dose aspirin or low-molecular-weight heparin may be recommended for pregnant women with ET to prevent blood clots. These drugs have a lower risk of causing side effects to the fetus. If the platelet count becomes too high (for example, $\geq 1500 \times 10^9$/L), or in the case of major bleeding, interferon can also be used safely during pregnancy. The patient's hematologist-oncologist should speak with the obstetrician about the best time to discontinue anti-platelet treatment prior to delivery. After giving birth, the doctor may recommend continuing heparin for few weeks to prevent deep vein thrombosis (DVT).

Very High Platelet Count. Younger patients with a low risk for clotting but with extremely high platelet counts (over 2 million platelets per microliter of blood) have an increased risk of bleeding. In these cases, use of medications to lower the platelet count should be considered. Aspirin should be avoided, at least until the platelet count has been reduced, as it may contribute to hemorrhaging, the loss of a large amount of blood in a short time.

Research and Clinical Trials

New treatment approaches for ET are under study in clinical trials, many of which are supported by LLS research programs.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of the standard treatment for a disease. Clinical trials are carefully designed and reviewed by expert clinicians and researchers as well as patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time you discuss treatment with your doctor. Patient participation in past clinical trials has resulted in the FDA-approved therapies we have today.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and their caregivers can speak with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit the LLS

Clinical Trial Support Center webpage at www. LLS.org/CTSC for more information.

Research Approaches. There are clinical trials for ET patients in a number of different situations, whether they are newly diagnosed, have advanced-stage disease, or are intolerant or resistant to their current medications. Sometimes, a clinical trial is the best treatment option for a patient. Researchers are currently studying:

- Specific gene mutations and cell signaling pathways involved in the development of ET, to help develop new targeted therapies for ET
- New treatments to reduce the risk of thrombosis and cardiovascular complications and to improve quality of life for ET patients
- New therapies to prevent ET from progressing to a more serious type of blood disease
- New treatments to help high-risk category ET patients live a normal life span

Drugs being researched for use in ET treatment include:

Peginterferon alfa-2a (Pegasys®). In the past, the use of interferon was restricted because it was not well tolerated by patients. However, there is new of interest in peginterferon's ability to induce a molecular response (remission) in some patients. This type of treatment response occurs when there is a decrease in the number of abnormal blood cells with genetic mutations. New formulations of peginterferon are being studied that may be better tolerated by patients than older formulations. Ongoing studies are comparing peginterferon alfa-2a with hydroxyurea in patients with ET. Researchers are also trying to determine if achieving a molecular response with interferon reduces the risk of ET progressing to myelofibrosis or acute myeloid leukemia.

Ruxolitinib (Jakafi®). This drug has been shown to be effective in patients with polycythemia vera and primary myelofibrosis. Researchers are now studying the use of ruxolitinib in patients with ET who are refractory or intolerant to hydroxyurea, to see whether it decreases platelet counts and disease-related symptoms.

Bomedemstat (IMG-7289). This drug inhibits lysine-specific demethylase 1 (LSD1), an enzyme essential for the production and function of megakaryocytes, so it prevents excess platelet production. The FDA has granted a "Fast Track" designation for the development of bomedemstat for the treatment of ET. This FDA process is designed to facilitate the development and expedite the review of drugs to treat serious conditions that fill an unmet medical need. Its purpose is to make important new drugs available to patients sooner.

Aspirin. Researchers are evaluating the effects of aspirin regimens using two

or three doses per day, compared to once-daily aspirin regimens, to prevent thrombosis in patients with intermediate-risk and high-risk ET.

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 a myelodysplastic syndrome.

Incidence, Causes and Risk Factors

ET is a rare blood disease. In the United States, the age-adjusted incidence rate of ET was approximately 1.5 per 100,000 persons in 2013-2017. Females are more likely to be diagnosed with ET than males. The median age at diagnosis is between 50 and 60 years, although young people, including women in their childbearing years, can develop it as well.

The cause of ET is not fully understood. Most cases of ET are associated with one or more acquired genetic mutations to a hematopoietic (blood) stem cell. This results in the overproduction of megakaryocytes, the cells that form platelets in the bone marrow. These mutations are not inherited; rather they occur during a person's lifetime. ET has been found to run in families in some cases. However, people seem to inherit an increased risk of developing ET, not the disease itself.

Myelofibrosis

Myelofibrosis (MF) is a rare type of blood cancer 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. As a result, the spleen and liver may begin to produce blood cells and increase in size. MF is sometimes also called "agnogenic myeloid metaplasia," "chronic idiopathic myelofibrosis," and "myelosclerosis with myeloid metaplasia."

When myelofibrosis develops on its own (and not as the result of another bone marrow disease) it is called "primary myelofibrosis." In other cases, another type of MPN, such as polycythemia vera (PV) or essential thrombocythemia (ET), can transform into MF. In these cases, it is known as "secondary MF," which may also be referred to as a "post-PV MF" or "post-ET MF." Between 10 and 20 percent of all MF cases begin as either PV or ET.

In many people, MF gets worse over time. Approximately 10-20 percent of all cases develop into acute myeloid leukemia (AML), an aggressive form of blood cancer. However, some patients with MF live symptom-free for years.

How MF Develops. Blood cells form in the bone marrow, where they begin as immature blood 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.

The cause of primary MF is not fully understood. It is a complex disease that may have many contributing factors. Researchers believe that proteins known as Janus kinases (JAKs) are involved. These proteins send signals 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. 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." Gene mutations in blood stem cells are thought to be responsible for the overactive JAK signaling that causes MF. The mutations may be in the genes that make JAKs, or in the genes that affect how JAKs work.

As the mutated overactive blood stem cell divides and makes copies of itself, it multiplies uncontrollably, creating many abnormal megakaryocytes in the bone marrow. (Megakaryocytes are the cells that produce platelets). These abnormal megakaryocytes may change the environment of the bone marrow by releasing cytokines. Some researchers believe this may cause inflammation and stimulate the buildup of fibrous tissue in the bone marrow. The web of fibers inside the bone marrow then becomes thick, like scar tissue.

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 red blood cells, this often causes anemia. Symptoms of anemia include fatigue, weakness and shortness of breath. When the bone marrow cannot 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, called "extramedullary hematopoiesis," often causes the spleen and the liver to become enlarged.

Signs and Symptoms

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

Patients with signs and symptoms of MF are referred to a hematologist-oncologist. A hematologist is a doctor who has special training in blood disorders, and an oncologist is a doctor who has special training in cancer. A hematologist-oncologist specializes in diagnosing and treating blood cancers.

MF 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, the bone marrow is unable to produce enough normal blood cells. The lack of 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
- Itching skin
- Fever
- Bone or joint pain
- Weight loss

When MF causes symptoms, they can be troublesome. Reducing symptoms is a key goal of treatment. Therefore, it is important to take an active role in monitoring your MF 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 that you and your doctor can use to evaluate your symptoms is by using the Myeloproliferative Neoplasm Symptom Assessment Form (see **Table 6** below). 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 MF be assessed both before and during treatment. Worsening symptoms can be a sign of disease progression and should be reported promptly to the doctor.

Table 6. 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: MPD, myeloproliferative disorder.
Adapted from Emanuel RM, et al. *Journal of Clinical Oncology*. 2012. National Comprehensive Cancer Network (NCCN). Guidelines for Physicians. *Myeloproliferative Neoplasms.* 2021. (Please see References.)

Complications

In medicine, a complication is a medical problem that occurs during the course of a disease or after a procedure or treatment. Possible complications of MF include:

- **Bleeding.** As MF progresses, your platelet level may drop below normal. The lack of platelets can cause bleeding to occur more easily than usual. Patients need to discuss bleeding concerns with their doctors when planning to have surgery or another medical procedure.
- **Abdominal and back pain.** An enlarged spleen can cause pain if it pushes up against other organs.
- **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.
- **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 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 may cause bleeding in the gastrointestinal (GI) system, coughing or spitting up blood, compression of the spinal cord, or seizures.
- **Bone and joint pain.** MF may lead to hardening 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. MF 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.
- **Acute myeloid leukemia (AML).** In about 10 to 20 percent of patients with MF, the disease eventually transforms into AML, a type of blood and bone marrow cancer that progresses rapidly.

Diagnostic Tests

While certain signs and symptoms may indicate that a person has MF, 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

Some of these tests may be repeated both during and after treatment to evaluate the effectiveness of treatment.

Medical History and Physical Examination. If a person has signs or symptoms of MF, the doctor will take a detailed medical history and do a 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 and other treatments
- History of thrombus (blood clot) or hemorrhagic events (loss of blood from damaged blood vessels)
- Medical history of blood relatives (because some illnesses run in families)
- Current symptoms

After completing the medical history, the doctor will conduct a physical examination. During the exam, the doctor may listen to your lungs and heart and carefully examine your body for signs of infection and disease. The doctor may also check to see if different organs of the body 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 measures the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin, the iron-rich protein that carries oxygen in red blood cells, and the hematocrit, the percent 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 MF often have an abnormally low level of red blood cells. Their white blood cell count is

usually higher than normal (a condition called “leukocytosis”), but in some cases it is lower than normal (called “leukopenia”). And their platelet count may be higher or lower than normal.

Peripheral Blood Smear. In this procedure, a sample of blood is viewed under a microscope to see if there are any unusual changes in the size, shape or appearance of various types of blood cells in the sample. 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-shape red blood cells as well as immature blast cells in their blood.

Blood Chemistry Profile. This blood test measures 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. People with MF often have elevated serum levels of uric acid, lactic dehydrogenase (LDH), alkaline phosphatase and bilirubin. The doctor may also check the serum levels of erythropoietin, ferritin, and iron, as well as the total iron binding capacity.

Bone Marrow Aspiration and Biopsy. These are two procedures that 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 using two different needles, 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 (aspirate) 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 3** on page 44 for more information on blood and bone marrow tests.

The samples are 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 differentiate MF from other types of MPNs. Patients with MF typically have increased number of megakaryocytes that are unusual in size and shape and the bone marrow has developed fibrosis.

In some MF patients, 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 that no cells can be obtained for this test.

Figure 3. 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.

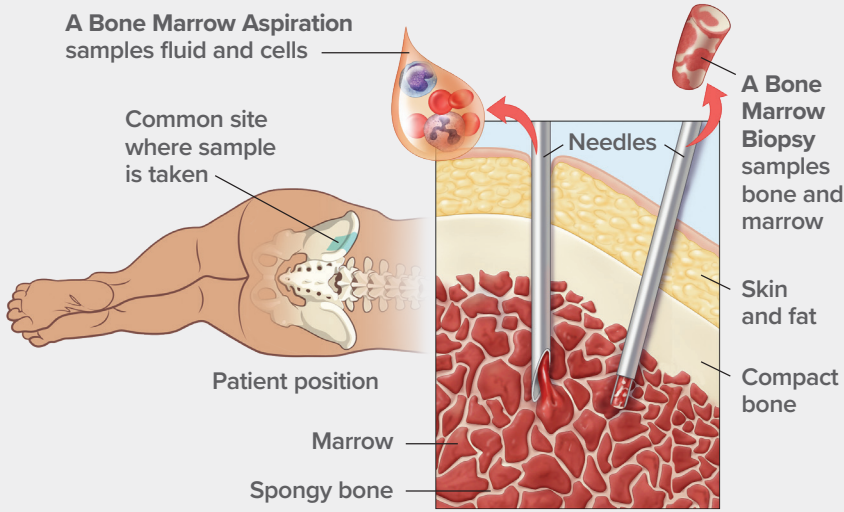
Bone Marrow Aspiration. A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

Bone Marrow Biopsy. A very small amount of bone filled with bone 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 procedue. They get medication first to numb the part of the body that will be used to get the sample of cells. Some patients are given a drug that makes them "sleep" during this procedure. 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. A 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 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.

Molecular Tests. These tests look for abnormal changes in the genes, chromosomes, proteins or other molecules within the patient's cancer cells. They are used for diagnosis and treatment planning.

Cytogenetic analysis (karyotyping). This test is used to look for abnormal changes in the chromosomes of the cancer cells. 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. 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.

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 essentially amplifies (increases) small amounts of specific pieces of DNA so that 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.

DNA sequencing. This term refers to a number of different laboratory tests that examine the exact sequence (order) of DNA. By comparing the sequence of DNA in cancer cells with the DNA in normal cells, doctors can find genetic changes that are unique to the cancer cells and may be driving the growth of the patient's cancer. DNA sequencing can be done with blood or bone marrow samples.

Approximately 90% 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 — 20-35%
- *MPL* mutation — 5-8%

About 10 percent of MF patients 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). Further study is needed to identify other gene mutations that may be involved.

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 Typing. This blood test should be performed in patients who are candidates for allogeneic stem cell transplantation. 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. It is not used to diagnose MF, but it is an important test for MF patients if allogeneic stem cell transplantation is being considered as a treatment option (see page 50 for more information on allogeneic stem cell transplantation).

Diagnosis

In 2016, the World Health Organization (WHO) published new criteria for diagnosing primary MF. These criteria are summarized in **Table 7**, below. For a diagnosis of MF to be made, all three of the "major criteria" and at least one of the "minor criteria" must be met.

Table 7. World Health Organization Diagnostic Criteria for MF

Myelofibrosis Diagnosis requires all 3 major criteria + at least 1 minor criteria
Major Criteria
1. Proliferation of abnormal megakaryocytes, accompanied by fibrosis in the bone marrow
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, **or** • Presence of immature blood cells in the peripheral blood (called "leukoerythroblastosis")

Prognostic Factors. Certain factors can affect a patient's prognosis — their 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 or not 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 three most common ones are the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS) and the DIPSS Plus. The DIPSS-Plus scoring system is shown in **Table 8** below.

Table 8. DIPSS-Plus Scoring System

Risk Factor	Points
Age >65 years	1
Constitutional symptoms	1
Hemoglobin <10 g/dL	1
White blood cell count >25 x 10^9/L	1
Peripheral blood blasts >1%	1
Platelet count <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or one or two chromosomal abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, inv(3) or 11q23 rearrangement.

See page 64 for an explanation of "constitutional symptoms."

The DIPSS-Plus categorizes patients into four risk groups based on these eight risk factors. For each factor that a patient has, one point is assessed. The points are totaled to determine the score and corresponding risk group for the patient, as follows:

- 0 points = low risk
- 1 point = intermediate-1 (INT-1) risk
- 2 or 3 points = intermediate-2 (INT-2) risk
- 4 or more points = high risk

A DIPSS-PLUS score calculator can be found online at: **https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-meylofibrosis**

Researchers are also beginning to assess genetic mutations as a prognostic factor in patients with MF. The Mutation-Enhanced International Prognostic Scoring

System 70 (MIPSS70) incorporates the clinical characteristics of the patient's disease and 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 cytogenetic information; the new version is the MIPSS70+ Version 2.0. As researchers learn more about the genetic factors involved in MF, they will use this information for treatment planning.

An MIPSS-70 score calculator can be found online at: **http://www.mipss70score.it**

Treatment Options

New treatments may have been approved since this book 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

The treatment approach for primary MF is the same as it is for both the post-PV and post-ET forms of the disease. However, there is no single treatment that is effective for all MF patients. Patients have varying symptoms and circumstances that require different treatment options. Some MF patients remain symptom-free for many years and do not require immediate treatment. All MF patients, however, need to be closely monitored.

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 MF patients. For most people with MF, 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, as summarized below.

Low 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 people 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 may be started if symptoms appear.

Low 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:

- Ruxolitinib (Jakafi®)
- Interferon alfa (Intron® A, Roferon®-A, and Pegasys®), although the best use of these medications may be in a clinical trial
- Hydroxyurea (Hydrea®)

Intermediate-1 (INT-1) Risk With Symptoms: For patients in the INT-1 risk category who have symptoms, treatment may include:

- Ruxolitinib (Jakafi®)
- Allogeneic stem cell transplantation (in some cases)

Intermediate-2 (INT-2) and High Risk: For patients in the INT-2 and high-risk categories who have symptoms, treatment may include:

- Ruxolitinib (Jakafi®)
- Fedratinib (Inrebic®)
- Allogeneic stem cell transplantation (for eligible patients, the transplant may begin shortly after diagnosis)
- Treatment for anemia (see *Supportive Care* on page 51 for more information)

Patients with intermediate-risk (INT-1 and INT-2) or high-risk MF should consider meeting with a transplant specialist to learn about stem cell transplantation and donor options in case they need a transplant in the future. For more information on allogeneic stem cell transplantation, see page 50.

Drug Therapies. The drugs used to treat MF patients include:

- **Ruxolitinib (Jakafi®).** This is a prescription JAK1/JAK2 inhibitor that is available as a pill. It is approved by the Food and Drug Administration (FDA) for the treatment of intermediate-risk or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults. The most common side effects are low platelet and red blood cell counts, bruising, dizziness and headaches. This oral drug is not associated with major toxicity. However, over time it may slightly increase the risk of infectious complications, such as pneumonia and urinary tract infections, as well as shingles.

- **Fedratinib (Inrebic®).** This oral JAK2 inhibitor is FDA-approved for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. According to NCCN and other journal articles, fedratinib is prescribed as a first-line treatment for patients with MF who have not already taken a JAK inhibitor, or as a second line treatment for patients with MF who are resistant or intolerant to ruxolitinib. It has been shown to reduce spleen size and symptom burden in some patients. Common side effects include low blood counts, nausea, vomiting, diarrhea, loss of appetite and elevated liver enzymes.
- **Hydroxyurea (Hydrea®).** This chemotherapy drug is taken by mouth as a pill or capsule. Although it is not FDA-approved for the treatment of MF, it may be prescribed to help reduce spleen size or high platelet and white blood cell counts in patients who are not eligible for allogeneic stem cell transplantation, or who cannot take ruxolitinib or fedratinib. Common side effects include low white blood cell count (which increases the risk of infection), low platelet counts (which increase the risk of bleeding), nausea, vomiting, diarrhea and ulcers in the mouth.
- **Interferon alfa (Intron® A, Roferon®-A, Pegasys®).** This drug, given by subcutaneous injection, is a synthetic version of a substance made by cells in the body to fight infections and tumor cells. It has been used to treat an enlarged spleen, bone pain and high platelet count in certain MF patients. Due to its effects on the immune system, interferon alfa may worsen thyroid abnormalities, diabetes mellitus or autoimmune diseases, and may also cause or worsen depression.

Allogeneic Stem Cell Transplantation. This is currently the only treatment that has the potential to cure MF, but it also carries a high risk of life-threatening side effects. It is a treatment option for patients with intermediate-2 and high-risk MF. It may also be an option for intermediate-1 risk category patients with low platelet counts or complex cytogenetics.

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, including normal blood-forming cells (called “blood stem cells”). After the conditioning treatment is completed, patients receive an infusion of blood stem cells from a matched or partially matched donor who may be either related or unrelated to the patient. The transplanted stem cells travel to the patient’s bone marrow, replacing the defective stem cells. 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 creates a new immune system for the patient that helps the body fight infections and other diseases. The new immune system also has the potential to recognize and attack any remaining cancer cells in the

body. The transplanted immune cells (called the "graft") identify the leukemia cells as foreign and destroy them. This is called the "graft-versus-leukemia (GVL) effect."

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.

One possible serious side effect of allogeneic stem cell transplantation is graft-versus-host disease (GVHD). This occurs when the transplanted donor immune cells (the graft) identify the cells in the recipient's body (the host) as foreign and attack them. The parts of the body most commonly damaged by GVHD include the skin, liver, stomach, intestines and eyes. It can develop within weeks after transplantation or much later. A doctor can order medications to help prevent or minimize the complications of GVHD.

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 or "nonmyeloablative" 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 the patient's bone marrow. 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.

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.

See the free LLS booklets *Blood and Marrow Stem Cell Transplantation*, *Cord Blood Stem Cell Transplantation Facts* and *Graft-Versus-Host Disease* for more information.

Supportive Care

Supportive care is given to improve the quality of life for patients with MF and other types of serious illnesses. The goal of supportive care is to prevent or treat the symptoms of MF.

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

For patients with a serum EPO level lower than 500 mU/mL, treatment may 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.

For patients with a serum EPO level of 500 mU/mL or higher, treatment may include:

- 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.

Splenomegaly (Enlarged Spleen). Many patients with 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 are JAK inhibitors given by mouth that 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.
- Interferon alfa (Intron® A, Roferon®-A, 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.

- Benefits include a reduction of symptoms, decreased portal hypertension and less need for red blood cell transfusions.
- Possible risks include bleeding, blood clots, infection, liver enlargement and an increased platelet count.

- Radiation therapy, which uses high powered x-rays to shrink the spleen. When other treatment methods 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 MF patients 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). The chemotherapy drug hydroxyurea may be given to reduce the high platelet and white blood cell counts. It may also help treat other MF symptoms, including an enlarged spleen, night sweats and weight loss. Patients with low blood cell counts or severe anemia should not take hydroxyurea.

Treatment Monitoring

The goal of treatment for MF is to reduce symptoms and minimize the risk of transformation to AML. You will have frequent doctor appointments after you start treatment. 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 that your symptoms are increasing and the disease is progressing, a bone marrow aspiration and biopsy should be performed as clinically indicated.

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 40).

Research and Clinical Trials

New treatment approaches for MF are under study in clinical trials, many of which are supported by LLS research programs.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of the standard treatment for a disease. Clinical trials are carefully designed and reviewed by expert clinicians and researchers as well as patient advocates to ensure safety and scientific

accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time you discuss treatment with your doctor. Patient participation in past clinical trials has resulted in the FDA-approved therapies we have today.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial in an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and their caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit the LLS Clinical Trial Support Center webpage at www. LLS.org/CTSC for more information.

Research on Treatment Approaches. There are clinical trials for MF patients in a number of different situations, whether they are newly diagnosed, have advanced-stage disease, or are intolerant or resistant to their current medications. Sometimes, a clinical trial is the best option for a patient.

Drugs being researched for use in treatment of MF include:

- **Momelotinib, luspatercept and sotatercept.** Use of these drugs is being studied to help patients with chronic anemia.
- **Pacritinib (SB1518).** This drug is being studied to help patients with severe low platelet counts.
- **Bomedemstat (IMG-7289).** This drug is being studied to help patients with high platelet counts.
- **JAK inhibitors.** In current clinical trials, drugs called “JAK inhibitors” are showing effectiveness in reducing spleen size and symptoms such as night sweats and fatigue, and possibly improving anemia. Pacritinib (SB1518) is being studied to lower platelet counts, and momelotinib is being studied for the treatment of anemia.
- **Antifibrotic agents.** These agents interfere with the process of tissue repair and fibrosis. PRM-151 is an antifibrotic therapy that is being tested to see whether it prevents and/or reverses fibrosis in patients with MF. Lysyl oxidase (LOX) and lysyl oxidase-like (LOXL) are other antifibrotic medications being studied in a clinical trials.
- **Telomerase inhibitor.** A drug called “imetelstat” is being studied for use in MF treatment to improve bone marrow fibrosis, bone marrow function and blood cell counts.
- **Panobinostat, pracinostat, umbralisib, bomdestat and navitoclax.** For patients who no longer respond to ruxolitinib, researchers are studying the use of these drugs, either in combination with ruxolitinib or as single-agent therapies.

Researchers continue to study treatments that not only reduce the symptoms of MF, but also modify the disease course.

Treatment Outcomes

Among patients with MF, the prognosis (meaning the likely outcome of the disease) varies widely. Each patient's risk factors are evaluated individually to determine their prognosis.

The approximate median survival for MF patients is as follows, based on their risk category:

- 15.4 years for low-risk category patients
- 6.5 years for intermediate-1 (INT-1) risk category patients
- 2.9 years for INT-2 risk category patients
- 1.3 years for high-risk category patients

However, 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 MF 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.

Incidence, Causes and Risk Factors

Incidence. MF is a rare blood disorder. The age-adjusted incidence rate of primary MF was approximately 0.4 per 100,000 people in the United States in 2013-2017. Primary MF is most commonly diagnosed in people 60-70 years old, but it can occur at any age. The median age at diagnosis is 67 years.

In general, the genetic mutations in MF are acquired during a person's lifetime. They are not inherited from a parent. The mutations may be caused by environmental factors, or they may occur during an error in cell division. In rare cases, MF has been found to run in some families. However, people seem to inherit an increased risk of MF, not the disease itself.

Risk Factors. A risk factor is anything that increases a person's chance of developing a disease. Although the causes of the genetic mutations associated with MF are often unknown, there are certain factors that are known to increase a person's risk of developing MF. These risk factors include:

- Age. While MF can occur at any age, it is most commonly diagnosed in people 50 years and older. The risk of getting MF increases with age.

- Prior MPN. In a small number of patients, MF develops from another type of MPN — either polycythemia vera (PV) or essential thrombocythemia (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 MF.

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, the most common blood protein
  - Blood-clotting proteins (coagulation factors) made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B12
- 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." The blood cells are suspended in the plasma. See **Figure 4** on page 57.

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

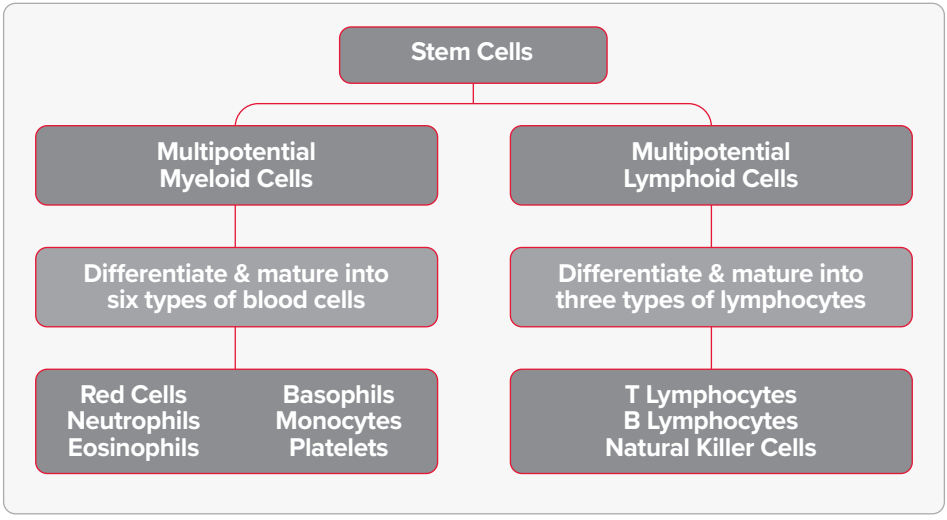
1. Red blood cells (the cells that carry oxygen)
   - These make up a little less than half of the body's total blood volume.
   - They are filled with hemoglobin, the protein that picks up oxygen from

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 (cells that help blood to clot)
   - These are small cells (one-tenth the size of red blood cells).
   - They help stop bleeding from an injury or cut.
   - They 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). These are the cells that fight infections. They include:
   - Neutrophils and monocytes. These cells, called "phagocytes," ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, neutrophils and 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. These WBCs, found mostly in the lymph nodes, spleen and lymphatic channels, 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 cells (NK cells)

Figure 4. Blood Cell & Lymphocyte Development



Bone Marrow. 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 blood passes through the 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, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make 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 harvested and used for future transplantation.

Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions and to make the most of the knowledge and skills of the members of your healthcare team.

For Help and Information

Consult With an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information.

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email and Live Chat: www.LLS.org/InformationSpecialists

Clinical Trial Support Center. Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find a clinical trial according to their needs and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Free Information Booklets. LLS offers free education and support booklets that can be either read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Please visit www.LLS.org/finances for more information.

***Co-Pay Assistance Program*.** LLS offers insurance premium and medication co-pay assistance for eligible patients. Please call or visit our website for more information.

- Call: (877) 557-2672
- Visit: www.LLS.org/copay

Free Mobile Apps

- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.
- LLS Coloring For Kids™ – Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian with experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Continuing Education. LLS offers free continuing education programs for healthcare professionals. Please visit www.LLS.org/ProfessionalEd for more information.

Community Resources and Networking

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients reach out and share information. Please visit www.LLS.org/chat to join.

LLS Chapters. LLS offers community support and services in the United States and Canada, including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact the nearest chapter, please call or visit our website.

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

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, please visit www.LLS.org/ResourceDirectory to obtain our directory.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. Please call or visit our website for more information.

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Additional Help for Specific Populations

Información en español (LLS Information in Spanish). Please visit www.LLS.org/espanol for more information.

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.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please call the VA or visit the webpage.

- Call: (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks who were subsequently diagnosed with a blood cancer may be eligible for 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 either in the NYC disaster area, or who lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please call the WTC Health Program or visit their webpage.

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

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a 2-week period. For more information, please call the National Institute of Mental Health (NIMH) or visit their website.

- Call: (866) 615-6464
- Visit: www.nimh.nih.gov and enter “depression” in the search box

Health Terms

Acquired Mutation. Type of mutation that occurs during a person's lifetime, rather than being inherited from a parent, and is present only in certain cells of the body. The mutation can be caused by environmental factors, or it may be caused by an error during cell division. Also called "somatic mutation."

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 that is 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.

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 (sugar) and enzymes.

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.

CBC. See Complete Blood Cell Count.

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 Disease. A disease or condition that usually lasts for a long period of time and may get worse over time.

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. CEL may progress slowly over many years, or it may progress quickly to an acute form of leukemia.

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.**

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. CNL may remain stable for many years, or it may progress quickly to an acute form of leukemia. **See the free LLS factsheet *Chronic Neutrophilic Leukemia Facts* 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.

Complete Blood Count (CBC). A laboratory test that measures the number of red blood cells, white blood cells and platelets in the blood. It also measures the amount of hemoglobin (the substance in the blood that carries oxygen) and the hematocrit (the amount of whole blood that is made up of red blood cells).

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

Constitutional Symptoms. Symptoms including fatigue, unexplained weight loss, night sweats and low-grade fever that affect the patient's general well-being.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes in cells. It detects chromosome alterations and, in some cases, may identify the actual genes that have been affected. These findings help doctors diagnose specific types of blood cancer, determine the best treatment approaches and monitor a patient's response to treatment.

Cytokine. A type of protein that affects the immune system. Some cytokines stimulate the immune system, while others slow it down.

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 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.

Eosinophil. A type of white blood cell that is released in the body when infections and allergic reactions occur.

Erythrocyte. See Red Blood Cell.

Erythropoietin (EPO). A hormone needed for normal production of red blood cells. It is made mainly by the kidneys and is released into the blood when blood oxygen levels fall below normal. Synthetic EPO is available in drugs called "erythropoiesis stimulating agents (ESAs)."

Essential Thrombocythemia. A rare cancer which the bone marrow produces too many platelets.

Extramedullary Hematopoiesis. The formation and development of blood cells outside the bone marrow.

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.

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.

Hematopoiesis. The formation and development of new blood cells in the bone marrow.

Hematopoietic Stem Cell. An immature cell that can develop into different types of blood cells, including red blood cells, white blood cells and platelets. Also called a "blood stem cell."

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."

Hemorrhage. Loss of blood from damaged blood vessels. A hemorrhage usually involves a lot of bleeding in a short period of time.

Hepatomegaly. An enlarged liver.

Human Leukocyte Antigen (HLA). A type of protein found on cells that helps the body distinguish its own cells from foreign cells. HLA factors are inherited from a person's mother and father. HLAs make up

a person's tissue type, which varies from person to person and are a critically important factor in allogeneic (donor) stem cell transplantation. Before transplantation takes place, tissue typing is performed in order to determine if the donor and recipient are compatible.

Hypercellularity. An abnormal excess of cells in the bone marrow.

Incidence. The number of new cases of a disease diagnosed each year.

***Janus kinase* (*JAK2*) gene.** This gene provides instructions for making a protein that promotes the growth and division of cells. The JAK2 protein is important for controlling the production of blood cells.

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

Lactate Dehydrogenase (LDH). One of a group of enzymes found in the blood and other body tissues that is involved in energy production in cells. An increased amount of LDH in the blood can be a sign of tissue damage, as well as certain types of cancer or other diseases.

Leukocyte. See White Blood Cell.

Leukocytosis. A condition in which the leukocyte (white blood cell) count is above normal in the blood.

Molecular Test. A laboratory test that checks for certain chromosome and gene changes, proteins or other molecules in a tissue sample.

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.

Myelofibrosis. A cancer in which abnormal blood cells and fibers build up inside the bone marrow.

Myeloproliferative Neoplasm (MPN). A blood disorder in which too many of certain types of blood cells are made in the bone marrow. There are a number of different types of MPNs, including polycythemia vera, essential thrombosis and myelofibrosis. MPNs usually become worse over time as the number of extra cells build up in the bone marrow and blood.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. The neutrophil is the main type of cell that combats infections.

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.

Peripheral Blood. The blood that circulates throughout the body in the arteries, capillaries and veins.

Peripheral Blood Smear. A procedure in which a sample of blood is examined under a microscope to determine the number of different types of blood cells in it, and to see whether the cells appear normal or abnormal.

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."

Plateletpheresis. 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 body.

Polycythemia Vera (PV). A cancer in which the bone marrow produces too many red blood cells, causing the blood to thicken abnormally. The numbers of white blood cells and platelets may also be above normal.

Portal Hypertension. High blood pressure in the portal vein that carries blood to the liver from the stomach, small and large intestines, spleen, pancreas and gallbladder. Portal hypertension may be caused by increased blood flow from an enlarged spleen or a blood clot that develops in the portal vein.

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

Pruritus. Severe itching.

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 the blood in healthy individuals. Also called "erythrocyte."

Reduced-Intensity Stem Cell Transplantation. A type of allogeneic stem cell transplantation in which patients receive lower doses of chemotherapy drugs and/or radiation as preparation for the transplant. The chemotherapy and radiation do not completely kill all the cancer cells. Instead, the new immune cells that the patient receives in the transplant may attack the cancer cells. This protocol may be safer than a traditional high-dose or myeloablative allogeneic stem cell transplant—especially for older patients. **See the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Refractory. The term used to describe a disease that does not go into remission or improve substantially after treatment.

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

Somatic Mutation. See Acquired Mutation.

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.

Splenectomy. A surgical procedure to remove the spleen.

Splenomegaly. An enlarged spleen.

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.

Thrombocytopenia. A condition characterized by having too few 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 a condition called "gout."

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

Venous Blood Clot. A blood clot in a vein.

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. Also called "leukocyte."

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