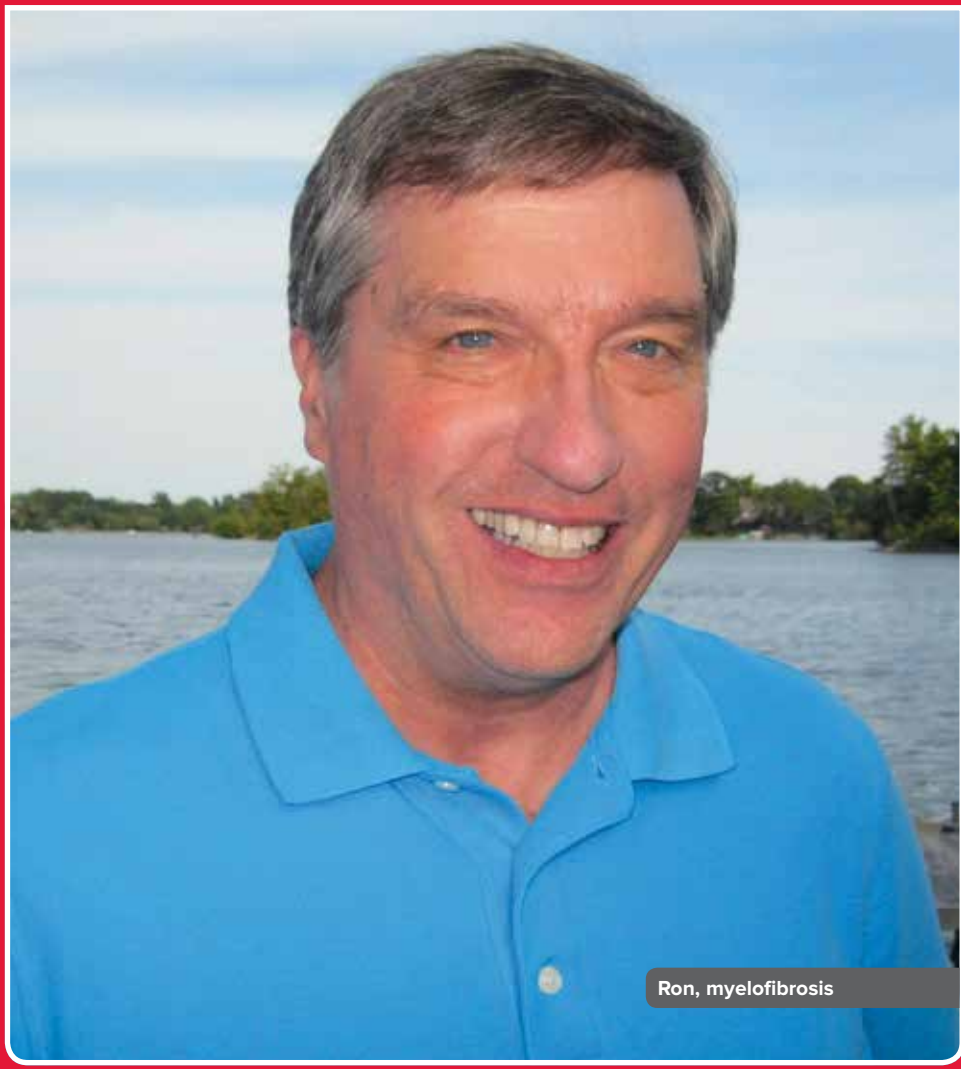
LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Myeloproliferative Neoplasms

Myelofibrosis, Polycythemia Vera and Essential Thrombocythemia



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A Message from Louis J. DeGennaro, PhD

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) is the world's largest voluntary health organization dedicated to finding cures for blood cancer patients. Our research grants have funded many of today's most promising advances; we are the leading source of free blood cancer information, education and support; and we advocate for blood cancer patients and their families, helping to ensure they have access to quality, affordable and coordinated care.

Since 1954, we have been a driving force behind almost every treatment breakthrough for blood cancer patients. We have invested more than $1 billion in research to advance therapies and save lives. Thanks to research and access to better treatments, survival rates for many blood cancer patients have doubled, tripled and even quadrupled.

Yet we are far from done.

Until there is a cure for cancer, we will continue to work hard—to fund new research, to create new patient programs and services, and to share information and resources about blood cancers.

This booklet has information that can help you understand myeloproliferative neoplasms, prepare your questions, find answers and resources, and communicate better with members of your healthcare team.

Our vision is that, one day, all people with myeloproliferative neoplasms will either be cured or will be able to manage their disease so that they can experience a great quality of life. Today, we hope our expertise, knowledge and resources will make a difference in your journey.

Louis J. DeGennaro, PhD
President and Chief Executive Officer
The Leukemia & Lymphoma Society

Inside this Booklet

Acknowledgement

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Introduction

This booklet provides information for patients and families about myeloproliferative neoplasms (MPNs). MPNs make up a group of blood diseases characterized by the overproduction of one or more types of blood cells—red blood cells, white blood cells and platelets. MPNs usually develop slowly over time, and different MPNs affect different blood cells. Many people with MPNs can experience few or no symptoms for extended periods of time with proper monitoring and treatment.

There are several types of MPNs. Three MPNs are traditionally grouped together because of their overlapping features. These three are often referred to as "classic" MPNs, "BCR-ABL fusion gene-negative" MPNs, or "Philadelphia-negative classical" MPNs. They are:

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

These three MPNs are rare diseases. In the United States, there are approximately 148,000 people living with polycythemia vera. An estimated 134,000 are living with essential thrombocythemia, and an estimated 13,000 have myelofibrosis.

This booklet will focus primarily on polycythemia vera, essential thrombocythemia and myelofibrosis: their symptoms, diagnosis and treatment. A brief description of normal blood and bone marrow, as well as a glossary of select health terms, is provided to help readers better understand these MPNs.

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 master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live online chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists

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

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

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

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. To join, visit www.LLS.org/community.

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

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), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- 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.

Clinical Trials (Research Studies). New treatments for patients are under way. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Advocacy. The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

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

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/especialistas.

Language Services. Let your doctor know if you need a language interpreter or other resource, such as a sign language interpreter. Often, these services are free.

Children. MPNs occur in a small number of children. Families face new and unfamiliar treatments and care protocols. The child, parents and siblings may all need support. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/booklets to receive the booklet *Coping with Childhood Leukemia and Lymphoma*
- Call: (800) 955-4572 to ask about *The Trish Greene Back to School Program for Children with Cancer*

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and 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: WTC Health Program at (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) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter the word depression in the search box

Feedback. To give suggestions about this booklet, visit www.LLS.org/publicationfeedback.

Myeloproliferative Neoplasms

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

- "Myelo" refers to bone marrow
- "Proliferative" means to grow or reproduce quickly
- "Neoplasm" is an abnormal growth of cells that occurs when cells divide more than they should or do not die when they should

Myeloproliferative neoplasms may be called by other names including myeloproliferative disease and chronic myeloproliferative neoplasms. There are several types of MPNs. Different MPNs affect different blood cells. This booklet provides information on the three classic types of MPNs that are traditionally grouped together because of their overlapping features. These three are:

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

Other types of MPNs include

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

These last four "other types of MPNs" are not covered in this book. For more information about chronic myeloid leukemia, see the free LLS booklet *Chronic Myeloid Leukemia*. For information on chronic neutrophilic leukemia, see the free LLS fact sheet *Chronic Neutrophilic Leukemia Facts.*

Causes of Myeloproliferative Neoplasms. MPNs are considered "clonal disorders." Clonal disorders begin with one or more changes to the DNA of a single stem cell in the bone marrow. An undeveloped stem cell, called a "hematopoietic" stem cell (HSC), is an immature blood cell that can develop into one of the three main types of blood cells: a red blood cell, a white blood cell or a platelet.

The changes to the immature (hematopoietic) stem cell cause the stem cell to reproduce continually, creating more and more abnormal stem cells and these abnormal cells become one or more types of blood cells. MPNs usually get worse over time as the number of extra blood cells build up in the bone marrow and bloodstream.

In most cases, the cause of the change to the stem cell is unknown. Mutations may be caused by environmental factors or by a mistake during cell division. While family clusters of PV, ET and MF have been reported, they are generally not inherited diseases. They arise from gene mutations that occur during a person's lifetime. These are called acquired (or somatic) mutations.

Many people with MPNs can experience few or no symptoms for extended periods with proper monitoring and treatment. Individuals with ET typically have a near-normal lifespan. People with PV may have a shorter-than-normal life span, but PV can usually be managed effectively for a long time. Patients with PV and ET, however, have the potential for their disease to progress to myelofibrosis, acute leukemia or myelodysplastic syndrome.

While life expectancy for MF may be shorter than it is for PV or ET, many patients with MF can remain comfortable and symptom-free for years with treatment. In others, MF can progress more quickly and require treatment to help relieve symptoms. Approximately 15 to 20 percent of patients with MF develop acute myeloid leukemia.

Polycythemia Vera

Polycythemia vera (PV) is an MPN in which too many red blood cells are made in the bone marrow. In many cases, the numbers of white blood cells and platelets are also elevated. With extra blood cells in the bloodstream, abnormal clots and bleeding are more likely to occur. This can increase the risk of heart attack, stroke (a clot that blocks blood flow to part of the brain which can damage brain tissue) or pulmonary embolism (blockage of an artery in the lungs). The extra blood cells can also accumulate in the spleen and cause the spleen to swell.

With careful medical supervision, PV can usually be managed effectively for many years. For some PV patients, however, the PV may progress to a more aggressive blood disease such as myelofibrosis, acute myeloid leukemia or myelodysplastic syndrome.

Incidence, Causes and Risk Factors for PV

Polycythemia vera is a rare blood disease. In the United States, the incidence (number of newly diagnosed cases) of PV is approximately 0.4 to 2.8 people per 100,000 persons per year. PV affects slightly more men than women. While PV can occur at any age, it is seen most often in individuals who are older than age 60.

The cause of PV is not fully understood. Researchers believe that proteins known as Janus kinases (JAKs) are involved. JAKs send signals that affect the production of blood cells in the bone marrow. These proteins help control the number of red blood cells, white blood cells and platelets. When JAKs send too many signals, they cause the bone marrow to make too many blood cells. This chain of events is referred to as overactive JAK signaling. JAK signaling may become overactive in many ways. One way is a mutation of the *JAK2* gene. Approximately 95 percent of PV patients have a mutation of the *JAK2* gene.

PV is associated with genetic changes that are somatic. This means that the genetic mutations are not inherited but 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; individuals seem to inherit an increased risk of PV but not the disease itself.

Signs and Symptoms of PV

PV develops slowly, and it may not cause symptoms for many years. The condition is often diagnosed during a routine blood test before severe symptoms occur.

Symptoms may include:

- Itchy skin, called "pruritus," especially after warm baths or showers
- Headaches

- Excessive sweating
- Blurred vision, double vision, or seeing dark or blind spots that come and go
- Ringing in the ears
- Fatigue
- Shortness of breath
- Weakness
- Dizziness
- Excessive bleeding or bruising
- Reddened skin
- Numbness, tingling or burning sensation in the feet
- Feeling of fullness or bloating in the left upper abdomen due to an enlarged spleen
- Weight loss for no known reason
- Painful inflammation in the joints caused by gout

Complications of PV. Possible complications of PV include:

- **Thrombosis (blood clots).** Abnormalities in the platelets increase a patient's risk of developing blood that is too thick and blood clots inside a blood vessel. Blood clots can block the flow of blood in the vessel, depriving tissues of normal blood flow and oxygen. Blood clots can cause stroke, heart attack or pulmonary embolism (blockage of an artery in the lungs). Blood clots occur in about 30 percent of patients even before PV is diagnosed.
- **Enlarged spleen.** The spleen is an organ located on the left side of the upper abdomen near the stomach and below the rib cage. The spleen filters the blood, stores blood cells and destroys old blood cells. The spleen may become abnormally enlarged in some individuals with PV because the spleen is working harder to manage the increased number of blood cells.
- **Other blood diseases.** In some cases, PV may progress to other related blood diseases including myelofibrosis, acute myeloid leukemia and, less commonly, myelodysplastic syndrome.

Diagnosis of PV

While a person may have certain signs and symptoms of PV, laboratory tests are needed to confirm the diagnosis. Generally, a doctor will consider other conditions first; sometimes a condition called "secondary polycythemia" is causing the increase in red blood cells. People with secondary polycythemia also have very high red blood cell counts, but unlike PV, polycythemia does not begin in the bone marrow and it is not a cancer. High red blood cell counts caused by polycythemia are a

reaction to another problem such as:

- High altitude
- Disease that leads to low oxygenation of the blood
- Kidney or liver tumor that secretes the hormone erythropoietin
- Inherited disease

Secondary polycythemia is managed primarily by treating the underlying condition causing the disorder. A patient with secondary polycythemia should have a return to normal red blood cell counts once the primary problem is successfully treated.

Medical History and Physical Examination. Patients with PV are usually referred to a hematologist-oncologist. The doctor starts with an evaluation of the patient which includes a detailed medical history and a physical examination.

This medical history should include information about the patient's

- Cardiovascular risk factors
- Past illnesses
- Injuries
- Treatments
- Medications
- A history of the formation or presence of blood clots inside a blood vessel (called "thrombosis") or loss of blood from damaged blood vessels (called "hemorrhagic events")
- History of blood relatives—some illnesses run in families
- Current symptoms

After the medical history, the doctor will conduct a physical examination. During the exam, the doctor may listen to the patient's lungs and heart and examine the patient's body for signs of infection and disease. The doctor may also feel different parts of the body, which is the medical way to examine organs, and check that they are normal sized, are soft or hard, or cause pain when touched. For example, the doctor may feel the abdomen to see if the patient has an enlarged spleen.

Next, blood and bone marrow tests are done to analyze a patient's blood and bone marrow cells. A pathologist, a doctor who specializes in identifying diseases by studying cells under a microscope, uses a variety of tests to analyze a patient's blood and bone marrow cells. The samples may also be examined by another type of doctor called a hematopathologist, a specialist who studies and diagnoses diseases of the blood.

Complete Blood Count (CBC). 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 the iron-rich protein that carries oxygen in red blood cells (the

hemoglobin) and the percent of whole blood made up of red blood cells (the hematocrit). People with PV have high red blood cell counts. They also often have

- Increased white blood cells and platelets
- Increased hemoglobin levels
- Increased hematocrit levels

Red Cell Mass Test. This procedure is used to measure 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 infrequently performed in the United States due to high cost, difficulty obtaining the appropriate test materials, and the advent of new blood tests such as mutational testing.

Peripheral Blood Smear. A procedure in which a blood sample is viewed under a microscope. A pathologist examines the sample to see if there are any unusual changes in the size, shape and appearance of various blood cells. The test also checks for the presence of immature (blast) cells in the blood.

Comprehensive Metabolic Panel. A group of blood tests that measure the levels of certain substances released into the blood by organs and tissues in the body (called the "blood chemistry profile"). These substances include electrolytes (such as sodium, potassium and chloride), fats, proteins, glucose (sugar) and enzymes. Blood chemistry tests provide important information about how well a person's kidneys, liver and other organs are working. For patients suspected of having PV, it is important to test the serum erythropoietin level. Erythropoietin is a hormone naturally produced by the kidneys to stimulate the production of new red blood cells. Individuals with PV usually have very low levels of erythropoietin.

Bone Marrow Aspiration and Biopsy. These tests are used to examine bone marrow cells, and are generally done at the same time. The samples are usually taken from the patient's hip bone after medicine has been given to numb the area. For a bone marrow aspiration, a hollow needle is inserted through the hip bone and into the bone marrow to remove a liquid sample of cells. For a bone marrow biopsy, a wider needle is used to remove a small piece of bone that contains marrow. Both samples are examined under a microscope to look for the presence and number of abnormal cells and the occurrence of scar tissue (called "fibrosis") in the bone marrow. In PV, the bone marrow shows above-normal numbers of blood cells and an abnormal number of the platelet-forming cells called "megakaryocytes" in the bone marrow. The pathologist also examines the chromosomes of the bone marrow cells to rule out other blood diseases.

Molecular Testing. Molecular genetic tests are very sensitive tests that look for specific gene mutations. If PV is suspected, molecular testing for the *JAK2* mutation should be performed. The *JAK2 V617F* mutation is found in more than 90 percent of PV patients. The U.S. Food and Drug Administration (FDA) has approved a test called ipsogen JAK2 RGQ PCR Kit to detect mutations affecting

the Janus Tyrosine Kinase 2 *(JAK2)* gene. This test is intended to help doctors evaluate patients for suspected PV.

The ipsogen JAK2 RGQ PCR Kit is a test that detects the *JAK2 V617F/G1849T* gene in DNA extracted from blood. The test is intended for use as an additional evaluation of suspected PV, together with other factors. This test does not detect less common mutations associated with PV (including mutations in *JAK exon 12*), and is not intended for stand-alone diagnosis of PV.

The *JAK exon12* mutation in the *JAK2* gene is found in 2-3 percent of PV patients. If there is high suspicion that a patient has PV but does not have the *JAK2 V617F* mutation, the patient should be tested for *JAK2 exon 12* and/or other uncommon mutations.

For more information about bone marrow tests and other lab tests, please see the free LLS publication *Understanding Lab and Imaging Tests.*

Criteria for Diagnosing Polycythemia Vera. In 2016, the World Health Organization published new criteria for diagnosing PV. The diagnosis of PV requires meeting all three major criteria (Major Criteria 1, 2, and 3 below), or the first two major criteria (Major Criteria 1 and 2 below) and the minor criterion.

Major Criteria 1. Very high red blood cell count, usually identified by either A, B, **or** C below:

- A. Hemoglobin level
  - Elevated levels of hemoglobin
    - Hemoglobin levels greater than 16.5 g/dL in men
    - Hemoglobin levels greater than 16.0 g/dL in women
- B. Hematocrit level
  - Elevated levels of hematocrit
    - Hematocrit greater than 49 percent in men
    - Hematocrit greater than 48 percent in women
- C. Red cell mass
  - Increased red cell mass

Major Criteria 2. Bone marrow biopsy (A **or** B below) showing:

- A. An abnormal excess of blood cells in the bone marrow (called "hypercellularity") with an elevation of red blood cells, white blood cells and platelets (called "panmyelosis")
- B. Proliferation of mature megakaryocytes that vary in size and shape

Major Criteria 3. Presence of the *JAK2V617F* or *JAK2 exon 12* gene mutation

Minor Criterion: Very low levels of erythropoietin

Treatment Planning for PV. Treatment decisions in PV are based on the patient's risk for clotting complications (thrombosis).

The two main risk factors for thrombosis are:

- A previous clot or clots
- Age 60 years or older

Patients are generally considered low risk if:

- They are younger than 60 years, **and**
- They have no history of thrombosis

Patients are generally considered high risk if:

- They are 60 years or older, **or**
- They have a history of thrombosis

Every patient's medical situation is different and should be evaluated individually by a hematologist-oncologist, a doctor who specializes in treating blood cancers. It is important for patients to discuss all treatment options with their medical team, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS publication *Choosing a Blood Cancer Specialist or Treatment Center*.

Treatment of PV

PV is a chronic disease. It is not curable, but it usually can be managed effectively for very long periods. The goal of therapy is to reduce the risk of thrombosis and to ease symptoms by lowering the number of extra blood cells.

Many treatment options are designed to manage PV by lowering hematocrit levels below 45 percent. Lower hematocrit targets have been proposed for women (42 percent), but researchers are still studying this recommendation. Careful medical supervision and therapy is important to keep the hematocrit concentration at normal levels.

Treatment for low-risk patients may include:

- Low-dose aspirin
- Therapeutic blood withdrawal (called "phlebotomy")

Treatment for high-risk patients may include:

- Low-dose aspirin
- Therapeutic phlebotomy
- Medication to reduce the number of blood cells ("cytoreductive" medication)

Low-Dose Aspirin. Low-dose aspirin may reduce the risk of blood clots. Low-dose aspirin helps prevent platelets from sticking together, making it less likely for blood clots to form. The most common side effects of aspirin are upset stomach and heartburn.

Therapeutic Phlebotomy. Most PV patients have their blood drawn at regular intervals. Blood is removed from the vein in a way that is similar to donating blood. Phlebotomy reduces the number of blood cells and decreases blood volume. After phlebotomy, the blood is thinner and less likely to cause "sludging," when red blood cells become massed along walls of blood vessels. The immediate effect of phlebotomy is the decrease of certain symptoms such as headaches, ringing in the ears and dizziness. Eventually, however, phlebotomy will result in iron deficiency.

Medications to Reduce the Number of Blood Cells. High-risk PV patients may be prescribed cytoreductive drugs to reduce the number of blood cells. These drugs may include any or a combination of the drugs listed below.

- **Hydroxyurea (Hydrea®)**—This chemotherapy drug is available as a pill. It is prescribed to help decrease the number of blood cells made in the bone marrow and to reduce the size of the spleen. It is used for high-risk patients, patients who cannot tolerate frequent phlebotomy, and for patients with high blood counts and enlarged spleens. Rare side effects are mouth ulcers, change in the sense of taste, skin ulcers or rash. There is some controversial data that long-term therapy with hydroxyurea is associated with an increased risk of acute leukemia, so it is frequently avoided as therapy for younger patients who have many years of treatment ahead of them.
- **Interferon alfa (Intron® A [alfa-2b] and Roferon®-A [alfa-2a]), and sustained-release preparations of these called PEG-Intron® ([peginterferon alfa-2b] and Pegasys® [peginterferon alfa-2a])**—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 of or resistant to hydroxyurea, or for younger patients for whom hydroxyurea is not recommended. Interferon is not used for most patients because, compared to other treatments for PV, it is less convenient to administer (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.
- **Ruxolitinib (Jakafi®)**—Ruxolitinib is a JAK1/JAK2 inhibitor approved by the Food and Drug Administration (FDA) as a second-line therapy to treat people

with PV who do not respond to or cannot take hydroxyurea. JAK proteins send signals that affect the production of blood cells in the bone marrow; when JAKs send too many signals, they cause the body to make too many blood cells. Ruxolitinib works by inhibiting the JAK proteins and reducing the overactive signaling. This oral drug is not associated with major toxicity but over time it may slightly increase the risk of infectious complications such as pneumonia and urinary tract infections as well as shingles.

- **Busulfan (Myleran®) and Chlorambucil (Leukeran®)**—These drugs may be prescribed for patients who cannot tolerate other medications. They are only prescribed to treat PV when other therapies have not been effective in patients at least 70 to 80 years old. Due to the risk of leukemia, they are not prescribed to younger patients.

Treatments to Reduce Itching. A troublesome symptom that occurs in many PV patients is itchy skin ("pruritus"). To help prevent itchiness, it is suggested that patients bathe less frequently, bathe or shower in cool water and use a gentle soap. Patients should also avoid hot tubs, heated whirlpools and hot showers or baths. It is also important to keep skin well moisturized with lotion and try not to scratch it because that can damage the skin. Antihistamines such as diphenhydramine (Benadryl®) may help itching that does not go away. Side effects of antihistamines include dry mouth, drowsiness, dizziness and restlessness. Other treatment options for itching include light therapy (phototherapy) using a medicine called psoralen combined with ultraviolet A (UVA) light.

For specific drug information, see the free LLS publication *Understanding Side Effects of Drug Therapy*, the LLS list of drugs at www.LLS.org/drugs, and the Food and Drug Administration (FDA) drug information website at https://www.accessdata.fda.gov/scripts/cder/daf/.

Treatment Side Effects in PV. The side effects of treatment for PV will depend on many factors, including the type of treatment and dosage, the age of the patient and coexisting medical conditions.

Side-effects management is important. Patients should discuss any concerns about side effects with their doctor. Most side effects are temporary and resolve when treatment is completed. For specific drug information, see the free LLS booklet *Understanding Side Effects of Drug Therapy*.

Special Considerations in PV. Patients with PV have increased risk for bleeding complications after surgery. Therefore, coordination between the patient's surgeon (your doctor who does the operation) and hematologist (the doctor who monitors your PV) is very important because the surgeon may not be aware of the patient's increased risks of bleeding and thrombosis. When surgery is elective, it is recommended that the patient's platelet and red blood counts have reached normal range before surgery. There should also be a plan to minimize the risk for excessive bleeding and deep vein thrombosis after surgery.

Taking Care of Yourself if You Have PV

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

- **Quit smoking.** Patients should stop smoking since tobacco makes blood vessels narrow and that can increase the risk of heart attack and stroke.
- **Aim for a healthy body weight.** Being overweight or obese increases the risk of developing high blood pressure, type 2 diabetes and coronary heart disease.
- **Take medications.** Some patients may need medications to lower blood pressure and cholesterol and to control diabetes. By controlling cholesterol, blood pressure and diabetes, a patient may decrease the chance of having a heart attack or stroke.
- **Exercise.** Moderate exercise such as walking can improve blood flow which decreases 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.

Research and Clinical Trials for PV

Patients are encouraged to explore clinical trials and enter one if they are eligible. Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the FDA as standard treatments.

Clinical Trials. Every new drug or treatment regimen goes through a series of clinical trials before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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. Sometimes, a clinical trial is the best option for a patient.

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 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:

- **Peginterferon alfa-2a (Pegasys®)**—In the past, the use of interferon has been restricted because it was not well tolerated by patients. Much interest, however, lies in interferon's ability to induce a molecular response in some patients. A molecular response occurs in PV patients when there is a reduction in the number of cells with the abnormal *JAK2* gene mutation. New formulations of interferon that may be effective in achieving a molecular remission with fewer side effects are now under study.
- **Givinostat**—Givinostat is a histone deacetylase (HDAC) inhibitor. HDAC inhibitors are substances which cause chemical changes that stop abnormal cells from growing or dividing. Researchers are studying whether givinostat is an effective second-line treatment for patients who are intolerant of or refractory to hydroxyurea. Researchers are also looking at combining givinostat with low-dose hydroxyurea.
- **Idasanutlin (RG7388)**—This is an oral MDM2 inhibitor that blocks specific protein interactions, and this inhibition results in upregulation of the p53 pathway. This is an important mechanism to induce program cell death (called "apoptosis") in PV cells.

Treatment Outcomes in PV

Median survival for PV patients is 10.9 years. People with PV may have a shorter-than-normal life span, but with careful medical supervision and therapy, PV can usually be managed effectively for a long time. In some cases, however, PV may progress to myelofibrosis, acute myeloid leukemia or myelodysplastic syndrome.

Essential Thrombocythemia

Essential thrombocythemia (ET) is an MPN in which the bone marrow produces too many platelets. Platelets are small cell fragments that stick together and form blood clots to slow or stop bleeding and to help heal wounds. Another word for platelet is "thrombocyte." When there are too many platelets, 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. ET may be called by other names including primary thrombocythemia, idiopathic thrombocythemia or primary thrombocytosis.

On average, individuals with ET have a normal life expectancy if they are properly monitored and treated. In a small number of patients, the disease may transform to myelofibrosis, acute myeloid leukemia or, less frequently, myelodysplastic syndrome.

Incidence, Causes and Risk Factors for ET

Essential thrombocythemia is a rare blood disease. In the United States, the incidence (newly diagnosed cases) of ET is approximately 0.38 to 1.7 per 100,000 persons. Women are more likely to be diagnosed with ET than men. The median age at diagnosis is 65 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 stem cell that results in the overproduction of megakaryocytes, the precursor cells of platelets in the bone marrow. These mutations are not inherited and occur during a person's lifetime. Less commonly, ET is inherited. When ET is inherited, it is called "familial essential thrombocythemia."

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

- *JAK2* mutation—60 percent
- *CALR* mutation—20-35 percent
- *MPL* mutation—1-4 percent

About 10 percent of ET patients do not have a *JAK2*, *MPL*, or *CALR* gene mutation. They are referred to as "triple-negative" ET. Further study is needed in triple-negative patients who have ET to identify other mutations that may cause their condition.

Signs and Symptoms of ET

Essential thrombocythemia is often detected during a routine blood test before an individual has any symptoms. One of the first indications of ET may be the development of a blood clot (thrombus). Signs and symptoms of ET include:

- Weakness
- Fainting
- Chest pain
- Burning or throbbing pain in the hands or feet caused by diminished blood flow (called "erythromelalgia")
- Enlarged spleen

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 serious condition is called a transient ischemic attack (TIA). Signs and symptoms of a TIA include:

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

In a small subset of patients, ET may cause bleeding. This may occur in patients with an extremely high platelet count. Signs and symptoms of bleeding may include:

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

In advanced cases of ET, additional symptoms may be present. These include

- Fatigue
- Weight loss
- Low-grade fevers
- Night sweats

Complications of ET. Abnormal blood clots that are a result of ET can lead to a variety of potentially serious complications including:

- **Stroke.** A clot that blocks blood flow to part of the brain. The loss of blood flow to the brain can damage brain tissue. Symptoms of a stroke include dizziness, numbness, weakness on one side of the body, and problems with talking, writing or understanding language.
- **Heart attack.** A clot that blocks blood flow to the heart.
- **Pregnancy complications.** Uncontrolled ET in pregnant women can lead to miscarriage, fetal growth retardation, premature delivery and premature separation of the placenta from the uterus (called "placental abruption").
- **Other blood diseases.** In some cases, ET patients can develop myelofibrosis, another MPN that results in bone scarring, anemia, and enlargement of the spleen and liver. In a smaller number of cases, ET may progress to myelodysplastic syndrome or acute myeloid leukemia.

Diagnosis of ET

While a person may have certain signs and symptoms of ET, laboratory tests are needed to confirm the diagnosis. Generally, a doctor will consider other factors first to determine if a condition called "reactive thrombocythemia" is causing an increase in platelets. Reactive thrombocythemia results in very high platelet counts, but unlike ET, it does not begin in the bone marrow. Instead, the high platelet count in reactive thrombocythemia is a reaction to another problem in the body such as:

- Inflammatory disease such as active arthritis or gastrointestinal (GI) inflammatory disease
- Iron deficiency anemia
- Undetected cancer
- Prior removal of the spleen (splenectomy)

A patient with reactive thrombocythemia will have a return to a normal platelet count once the primary problem is successfully treated.

Medical History and Physical Examination. Evaluation of an individual with suspected ET should start with a detailed medical history and a physical examination by a hematologist-oncologist.

The medical history should include information about the patient's

- Cardiovascular risk factors
- Past illnesses
- Injuries

- Treatments
- Medications
- A history of the formation or presence of a blood clot inside a blood vessel (thrombosis) or loss of blood from damaged blood vessels (hemorrhagic events)
- History of blood relatives—some illnesses run in families
- Current symptoms

After the medical history, the doctor will conduct a physical examination. During the physical examination, the doctor may listen to the patient's lungs and heart and examine the patient's body for signs of infection and disease. The doctor may also feel different parts of the body and check the organs to see if they are of normal size, are soft or hard, or cause pain when touched.

Next, blood and bone marrow tests are done to analyze a patient's blood and bone marrow cells. A pathologist, a doctor who specializes in identifying diseases by studying cells under a microscope, will use a variety of tests to analyze a patient's blood and bone marrow cells. The samples may also be examined by a hematopathologist, a specialist who studies and diagnoses blood diseases.

Complete Blood Count. This test measures the number red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of substance in the blood that carries oxygen (hemoglobin) and the percent of whole blood that is made up of red blood cells (hematocrit). In patients with ET, the platelet count is higher than normal.

Peripheral Blood Smear. A procedure in which a small amount of blood is viewed under a microscope. A pathologist examines the sample to see if there are any unusual changes in the size, shape or appearance of various blood cells. The test also checks for the presence of immature (blast) cells in the blood. In patients with ET, the platelets in the sample may appear enlarged and/or clumped together.

Comprehensive Metabolic Panel. 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. Blood chemistry tests give important information about how well a person's kidneys, liver and other organs are working. These tests are not used to diagnose ET, but an abnormal amount of a particular substance in the blood may be a sign of disease or other health problem.

Bone Marrow Aspiration and Biopsy. These tests are used to examine bone marrow cells and are generally done at the same time. The samples are usually taken from the patient's hip (pelvic) bone after medicine has been given to numb the hip area. For a bone marrow aspiration, a hollow needle is inserted through the hip bone and into the bone marrow to remove a liquid sample of cells. For a bone marrow biopsy, a wider needle is used to remove a small piece of bone that contains

marrow. Each sample is examined under a microscope to look for the presence of abnormal cells and the occurrence of scar tissue (fibrosis) in the bone marrow. In patients with ET, there are increased numbers of platelet-forming cells in the bone marrow (megakaryocytes). These megakaryocytes also appear abnormal in shape and size.

Molecular Testing. Molecular genetic tests are very sensitive tests that look for mutations in genes. In suspected cases of ET, doctors test for mutations of the *JAK2*, *MPL* and *CALR* genes.

Criteria for Diagnosing Essential Thrombocythemia. In 2016, the World Health Organization published new criteria for diagnosing ET. The diagnosis of ET requires meeting all four major criteria (Major Criteria 1, 2 ,3, 4) listed below, or the first three major criteria (Major Criteria 1, 2, and 3) and the one minor criterion listed below.

Four Major Criteria

1. Platelet count equal or greater than 450 × 10^9/L, **and**
2. Bone marrow biopsy showing increased numbers of platelet-forming cells (megakaryocytes) with abnormal nuclei, **and**
3. Exclusion of other diseases defined by World Health Organization 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, **and/or**

Minor Criterion

- Presence of a clonal marker (chromosome abnormality) **or** no evidence that the disorder is caused by reactive thrombocytosis

Treatment Planning for ET. Doctors consider various risk factors in treatment planning for ET. These factors are:

Conventional Score for Prediction of Vascular Complications (European LeukemiaNet)

- Low risk (none of the 3 major risk factors):
  - Age younger than 60 years, **and**
  - No history of thrombosis or major bleeding, **and**
  - Platelet count <1500 x10^9/L

- High risk (at least 1 of the 3 major risk factors)
  - Age 60 years or older, **and/or**
  - History of thrombosis or major bleed, **and/or**
  - Platelet count ≥1500 x10^9/L

International Prognostic Score for Thrombosis for Essential Thrombocythemia (ET) (IPSET-thrombosis)

- Patient age
  - Younger than 60 years (0 points)
  - Older than 60 years (1 point)
- Prior thrombotic event
  - No (0 points)
  - Yes (2 points)
- Cardiovascuar risk factors present
  - No (0 points)
  - Yes (1 point)
- *JAK2 V617* mutation detected
  - No (0 points)
  - Yes (2 points)

Score	Risk category
0-1	Low
2	Intermediate
3-6	High

For some patients with no sign of the disease other than an increased platelet count, the risk of complications may be low and no therapy needed. On the other hand, in patients with previous bleeding or clotting episodes and in patients who are at high risk for such complications, doctors may use medications to reduce high platelet counts.

Every patient's medical situation is different and should be evaluated individually by a hematologist-oncologist who specializes in treating blood cancers. It is important for patients and the members of their medical team to discuss all treatment options, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS publication *Choosing a Blood Cancer Specialist or Treatment Center.*

Treatment of ET

Prevention of blood clots (thrombosis) and bleeding (hemorrhaging) is the main objective of treating patients with ET. A hematologist can recommend specific treatments to manage ET.

For patients with low-risk disease and no symptoms, the risk of complications may be low. The doctor may prescribe low-dose aspirin or no therapy at all. The doctor will monitor the patient closely through regular exams, watching for any signs of disease progression.

For patients with high-risk disease, doctors may combine low-dose aspirin to prevent thrombosis and other medications to reduce high platelet counts.

Drug Therapy. The treatment of ET may include any or a combination of the following treatments listed below.

Low-Dose Aspirin. Low-dose aspirin may reduce the risk of clotting complications. Low-dose aspirin helps prevent platelets from sticking together, making it less likely for blood clots to form that 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.

Hydroxyurea (Hydrea®). This chemotherapy drug is available as a pill. It is prescribed to help decrease the number of blood cells made in the bone marrow. Hydroxyurea is often successful in decreasing the platelet count within several weeks, with few short-term side effects. In some patients, it may lower red blood cell counts, causing anemia. Other rare side effects are mouth ulcers, change in the sense of taste, skin ulcers or rash. There is some controversial evidence that hydroxyurea is associated with an increased risk of developing acute leukemia after long-term therapy and it is frequently therefore avoided as therapy for younger patients, who may need many years of treatment in the future.

Anagrelide (Agrylin®). This is an agent that does not kill cells (a "non-cytotoxic" drug), but rather, it decreases the body's production of platelets. Anagrelide is not associated with an increased risk of leukemia, but may not be as effective as hydroxyurea in reducing certain types of clots. Side effects of anagrelide include fluid retention, heart and blood pressure problems, headaches, dizziness, nausea and diarrhea.

Interferon alfa (Intron® A [alfa-2b] and Roferon®-A [alfa-2a]) and their associated sustained-release preparations PEG-Intron® ([peginterferon alfa-2b] and Pegasys® [peginterferon alfa-2a]). Interferon is another treatment for lowering platelet counts in patients with ET. It may be used for patients who are either intolerant of or resistant to hydroxyurea, or for younger patients for whom hydroxyurea is not recommended. However, it is not used in most patients because, compared with 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 (Busulfex®, Myleran®) and Pipobroman (Vercyte®). These drugs are used as second-line treatments in older patients who are unresponsive to or intolerant of hydroxyurea. These drugs are associated with an increased risk of developing acute leukemia after long-term use and are generally used in older patients.

Plateletpheresis. This is a process that uses a special machine to skim platelets from a patient's blood and then return the remaining blood components to the patient. 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.

Treatment Side Effects in ET. The side effects of treatment for ET will depend on many factors, including the type of treatment and dosage, the age of the patient and coexisting medical conditions.

Management of side effects is important. Patients should discuss any concerns about side effects with their doctor. Most side effects are temporary and resolve when treatment is completed. For specific drug information, see the free LLS booklet *Understanding Side Effects of Drug Therapy*.

Special Considerations in ET. Pregnancy and high platelet counts require special monitoring.

Pregnancy. In general, pregnancy increases a woman's risk of blood clots, and pregnant women with ET are particularly susceptible to blood clots. Due to the risks to the developing fetus, many medications used to treat ET should be avoided during pregnancy including hydroxyurea and anagrelide. Low-dose aspirin or low molecular weight heparin may be recommended to pregnant ET patients to prevent blood clots because 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 discuss with the obstetrician the best time to discontinue anti-platelet treatment prior to delivery. After birth, the doctor may recommend continuing with heparin for few weeks to prevent deep vein thrombosis (DVT).

Very High Platelet Counts. Younger patients with 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 an extremely high platelet count should be considered, but aspirin should be avoided, at least until the platelet count has been reduced, as it may contribute to hemorrhaging.

For specific drug information, see the free LLS publication *Understanding Side Effects of Drug Therapy*, the LLS list of drugs at www.LLS.org/drugs, and the Food and Drug Administration (FDA) drug information website at https://www.accessdata.fda.gov/scripts/cder/daf/.

Taking Care of Yourself if You Have ET

Patients with ET are at increased risk of thrombosis and cardiovascular events. A heart-healthy lifestyle may decrease the risk of thrombosis, strokes and heart attacks. Lifestyle changes may include:

- **Quit smoking.** Patients should stop smoking because tobacco makes blood vessels narrow, which can increase the risk of heart attack and stroke.
- **Aim for a healthy body weight.** Being overweight or obese increases the risk of developing high blood pressure, type 2 diabetes and coronary heart disease, which are risks for cardiovascular disease.
- **Take your medications.** Some patients may need medications to lower blood pressure and cholesterol and/or to control diabetes. By taking the medications that doctors prescribe for high cholesterol, high blood pressure, and diabetes, a patient can decrease the chance of having a heart attack or stroke.
- **Exercise.** Moderate exercise such as walking can improve blood flow, which decreases 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.

Research and Clinical Trials in ET

Patients are encouraged to explore clinical trials and enter one if they are eligible. Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the FDA as standard treatments.

Clinical Trials. Every new drug or treatment regimen goes through a series of clinical trials before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct

clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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. Sometimes, a clinical trial is the best option for a patient.

Although researchers have a better understanding of the genetic basis of ET, they are still trying to improve the management of this disorder. While low-dose aspirin combined with hydroxyurea may represent an acceptable treatment for patients older than age 60, there is a need for disease-modifying drugs for younger patients to stop or slow the progress of the disease and also prevent the development of a more serious blood disease. Drugs under investigation to reach these goals are included in the following list.

Peginterferon alfa-2a (Pegasys®). In the past, the use of interferon has been restricted because it was not well tolerated by patients. Much interest, however, lies in peginterferon's ability to induce a molecular response in some patients. A molecular response occurs when there is a reduction in the number of abnormal blood cells. New formulations of peginterferon are now under study that may be better tolerated than older forms. 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 evolving to myelofibrosis or acute myeloid leukemia.

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

Treatment Outcomes in ET

On average, individuals with ET have a near-normal life expectancy if they are properly monitored and treated. Very rarely, ET can transform to a more aggressive blood disease. Patients are advised to discuss survival information with their doctors.

Myelofibrosis

Myelofibrosis (MF) is a rare disorder in which abnormal blood cells and fibers build up in the bone marrow, the sponge-like tissue in the center of most bones. In the bone marrow, there are immature blood cells (hematopoietic stem cells) that can develop into one of the three main types of blood cells: red blood cells, white blood cells and platelets. Primary MF begins with one or more mutations to the DNA of a single hematopoietic stem cell. As the mutated stem cell copies itself and divides, it multiplies uncontrollably, creating many abnormal immature blood cells called "blasts." These blasts do not mature into healthy blood cells nor do they function as healthy blood cells. Over time, the creation of abnormal blasts surpasses the bone marrow's ability to produce normal healthy blood cells.

Researchers theorize that mutated hematopoietic stem cells may change the environment of the bone marrow by releasing chemicals that can cause the spongy bone marrow to become scarred (fibrous). The web of fibers inside the bone marrow becomes thick, like scar tissue. One blood cell thought to contribute to the fibrous tissue is the giant cell in the bone marrow called the "megakaryocyte." Huge megakaryocytes break up into fragments in the bone marrow and produce hundreds to thousands of platelets. With MF, the bone marrow creates too many abnormal megakaryocytes. These megakaryocytes release substances called "cytokines," which some researchers believe may cause inflammation and stimulate the buildup of more fibrous tissue in the bone marrow.

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, anemia often results. 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 getting an infection. A reduction in platelets can cause easy bleeding and bruising. 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.

Many people with MF get worse over time, and approximately 10-20 percent of all cases develop into acute myeloid leukemia, an aggressive form of blood cancer. On the other hand, some patients with MF live symptom-free for years.

If MF is a person's first MPN then it is known as primary MF. In other cases, another MPN such as polycythemia vera (PV) or essential thrombocythemia (ET) can transform and become MF. These conditions are known as secondary MF. They may also be referred to as post-PV MF and post-ET MF. Between 15 and 20 percent of MF cases begin as either PV or ET. MF is known by several other names, including agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis, and myelosclerosis with myeloid metaplasia.

Incidence, Causes and Risk Factors of MF

Incidence. Primary MF is a rare blood disorder. The incidence (newly diagnosed cases) of primary MF is approximately 0.1 to 1.0 per 100,000 people in the United States annually. Primary MF is most commonly diagnosed in people age 50 to 80, but it can occur at any age.

Causes. The cause of primary MF is not fully understood. Researchers believe that proteins known as Janus kinases (JAKs) are involved. JAKs send signals that affect the production of blood cells in the bone marrow. This protein helps 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. When JAKs send too many signals, however, they cause the bone marrow to make too many blood cells. This chain of events is referred to as "overactive JAK signaling." Mutations in genes of hematopoietic 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 the mutations may be in genes that affect how JAKs work.

The vast majority of patients with MF have either a mutation of the *JAK2*, *MPL*, or *CALR* gene. Estimates for the frequency at which these genes are mutated in MF are as follows:

- *JAK2* mutation—60 percent
- *CALR* mutation—20-35 percent
- *MPL* mutation—5-8 percent

About 10 percent of MF patients do not have a *JAK2*, *MPL*, or *CALR* gene mutation. They are referred to as "triple-negative" MF, and these cases are associated with a worse outcome (prognosis). Further study is needed in triple-negative MF patients to identify other genes that may be involved in their disorder.

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

In general, the genetic mutations in MF are acquired during a person's lifetime. These mutations are not inherited from a parent. The mutations may be caused by environmental factors, or they may occur during a mistake in cell division. In rare cases, MF has been found to run in families. In some families, individuals seem to inherit an increased risk of MF but 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 that are linked to MF are often unknown, there are certain risk factors that are known to increase a person's risk of developing MF. These include:

- Age. While MF can occur at any age, it is most commonly diagnosed in people ages 50 and older. The risk of getting MF increases with age.
- Prior MPN. In a small portion of patients with polycythemia vera or essential thrombocythemia, the disease progresses to MF.
- 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.

Signs and Symptoms of MF

MF usually develops slowly. MF often does not cause early symptoms and may be found during a routine blood test. As disruption of normal blood cell production increases, however, people may experience the following signs and symptoms:

- Fatigue, weakness, shortness of breath, or pale skin (usually due to a low red blood cell count causing anemia)
- Abdominal pain, feeling of fullness, decreased appetite and weight loss as a result of an enlarged spleen (splenomegaly)
- Enlarged liver (hepatomegaly)
- Easy bleeding or bruising, as a result of a low platelet count (thrombocytopenia)
- Night sweats
- Itching skin
- Fever
- Frequent infections, due to a low white blood cell count
- Bone or joint pain
- Weight loss

Complications of MF. As MF progresses, complications may arise. Some of these may include:

- **Bleeding**—As MF progresses, the number of platelets may drop below normal levels. Insufficient platelets can lead to bleeding more easily than usual. Patients need to discuss bleeding concerns with their doctors when planning to have surgery or other medical procedures.

- **Abdominal and Back Pain**—An enlarged spleen can cause pain when it pushes up against other organs.
- **Portal Hypertension**—Normally, blood flow from the spleen enters 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 the veins to rupture and bleed. Portal hypertension may also be caused by a blood clot that develops in the portal vein, which may obstruct the blood flow through it.
- **Extramedullary Hematopoiesis**—When the bone marrow is no longer able to make sufficient blood cells, other organs in the body such as the spleen may begin to produce blood cells. This often causes the spleen to become enlarged. Extramedullary hematopoiesis may also lead to the creation of clumps or tumors of developing blood cells in other areas of the body, which 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**—MF increases the body's production of uric acid. When uric acid builds up, it forms crystals in the joints causing sharp pain, swollen joints and inflammation.
- **Acute Myeloid Leukemia (AML)**—In about 15 to 20 percent of patients with MF, the disease will transform to AML, a type of blood and bone marrow cancer that progresses rapidly.

Diagnosis of MF

While a person may have certain signs and symptoms of MF, laboratory tests are needed to confirm the diagnosis. Generally, a doctor will consider other conditions first to determine if "reactive myelofibrosis" is causing the patient's disorder. Reactive myelofibrosis also results in scarring in the bone marrow, but unlike MF, it does not begin in the bone marrow. Instead, reactive myelofibrosis is a reaction to another problem in the body such as:

- Infection
- Autoimmune disorder
- Other chronic inflammatory conditions
- Hairy cell leukemia or other lymphoid neoplasm

Reactive myelofibrosis is reversible if the underlying cause can be successfully treated.

Evaluation of an individual with suspected MF should start with a detailed medical history and a physical examination.

Medical History and Physical Examination. The medical history should include information about the patient's

- Cardiovascular risk factors
- Past illnesses
- Injuries
- Treatments
- Medications
- History of thrombosis (the formation or presence of a blood clot inside a blood vessel) or hemorrhagic events (loss of blood from damaged blood vessels)
- History of blood relatives—some illnesses run in families
- Current symptoms

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

Next, specific tests are done to analyze the patient's blood and bone marrow cells. A pathologist, a doctor who specializes in identifying diseases by studying cells under a microscope, uses a variety of tests to analyze the patient's blood and marrow cells. The samples may also be examined by a hematopathologist, a specialist who studies and diagnoses diseases of the blood.

Complete Blood Count (CBC). This test is used to measure the number red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of the iron-rich protein that carries oxygen in red blood cells (hemoglobin) and the percent of whole blood made up of red blood cells (hematocrit). People with MF often have abnormally low levels of red blood cells. White blood cell counts are usually higher than normal (called "leukocytosis"), but in some patients, the white blood cell counts may be lower than normal (called "leukopenia"). Platelet counts may be higher or lower than normal.

Peripheral Blood Smear. A procedure in which a sample of blood is viewed under a microscope. A pathologist examines the size, shape, and appearance of blood cells in the sample, and also checks for the presence of blast cells (immature blood cells). Blast cells are normally found in the bone marrow and are not typically

found in the peripheral blood of healthy individuals. People with MF often have abnormal teardrop-shape red blood cells and immature blasts in the blood.

Comprehensive Metabolic Panel. The blood tests that comprise the metabolic panel 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. Blood chemistry tests give important information about how well a person's kidneys, liver and other organs are working. Individuals with MF often have elevated serum levels of uric acid, lactic dehydrogenase (LDH), alkaline phosphatase and bilirubin. The doctor may also check the levels of serum erythropoietin level, serum ferritin, iron, and total iron binding capacity.

Bone Marrow Aspiration and Biopsy. These tests are used to examine bone marrow and are generally done at the same time. The samples are usually taken from the patient's hip (pelvic) bone after medicine has been given to numb the area. For a bone marrow aspiration, a hollow needle is inserted through the hip bone and into the bone marrow to remove a liquid sample of cells. For a bone marrow biopsy, a wider needle is used to remove a small piece of bone that contains marrow. A pathologist studies the samples under the microscope and examines the chromosomes inside the cells. This is necessary to differentiate MF from other MPNs. Patients with MF have increased numbers of megakaryocytes that are also unusual in size and shape, and there is scarring of the bone marrow (fibrosis). For some MF patients, it is not possible to obtain a sample of the bone marrow fluid during a bone marrow aspiration due to the scaring in the bone marrow. The scarring will cause the aspiration to be "dry," meaning no cells are present.

Molecular Testing. Molecular genetic tests are very sensitive tests that look for specific gene mutations. The 2016 World Health Organization diagnostic criteria now include molecular testing for *JAK2*, *CALR*, and *MPL* mutations for individuals suspected of having MF. If the patient does not have one of these mutations, the doctor may test for other mutations.

Imaging Tests. Ultrasound tests may be used to determine the size of the spleen. Magnetic resonance imaging (MRI) tests may be used to identify changes in the bone marrow that indicate MF.

HLA Typing. HLA typing should be performed for patients who are candidates for an allogeneic stem cell transplantation. This is a blood test that determines a person's HLA type. 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. The 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. HLA matching is done prior to a donor stem cell transplantation to find out if tissues between the donor and the person receiving the transplant match. HLA is not used

to diagnose MF. It is, however, an important test for MF patients if an allogeneic stem cell transplantation is being considered as a treatment option.

Criteria for Diagnosing Primary Myelofibrosis. In 2016, the World Health Organization published new criteria for diagnosing primary MF. The diagnosis of primary MF requires meeting all three major criteria and at least one minor criterion listed below.

Three Major Criteria

1. Proliferation of abnormal megakaryocytes accompanied by fibrosis in the bone marrow
2. Exclusion of other diseases defined by World Health Organization 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")

Treatment Planning for MF. Certain factors affect prognosis and treatment options for patients with MF. Doctors use prognostic scoring systems to evaluate treatment options for patients. For MF, there are multiple scoring systems available to help doctors estimate a patient's "prognosis," which means the likely course of a disease; for example, a "good" prognosis is an optimistic outcome. The three most common prognostic scoring systems used for risk stratification are the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS), and DIPSS Plus.

The Dynamic International Prognostic Scoring System (DIPSS) Plus uses the following eight risk factors:

1. Age older than 65
2. Hemoglobin lower than 10 g/dL
3. Leukocytes greater than 25 x10^9/L

4. Circulating blast cells equal to or greater than 1 percent
5. Constitutional symptoms (fatigue, night sweats, fever, unexplained weight loss, etc)
6. The need for red blood cell transfusions
7. Platelet count less than 100 x10^9/L
8. Unfavorable karyotype (chromosome abnormalities)

DIPSS Plus stratifies patients into four risk groups based on these eight risk factors. Patients with no risk factors are classified as "low-risk." Patients with one risk factor are classified as "intermediate 1 risk" (INT-1); patients with two or three risk factors are classified as "intermediate 2 risk" (INT-2); and patients with four or more factors are classified as high-risk.

Researchers are also beginning to incorporate a patient's mutational status in assessing a patient's prognosis. For example, certain gene mutations in MF patients, such as the *CALR* mutation, are associated with better overall survival than those with *JAK2* or *MPL* mutations. As researchers learn more about the genetic factors involved in MF, they will use this information for treatment planning.

Every patient's medical situation is different and should be evaluated individually by a hematologist-oncologist, who specializes in treating blood cancers. Patients diagnosed with MF are encouraged to seek a referral to specialized centers with expertise in the management of MF. It is important for patients and their doctors to discuss all treatment options, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS booklet *Choosing a Blood Cancer Specialist or Treatment Center*.

Treatment of MF

The treatment approach for primary MF is the same as for post-polycythemia vera MF or post-essential thrombocythemia MF. There is, however, not one 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 potential cure for MF is allogeneic stem cell transplantation. But this procedure is risky for older patients and those with other health problems. Because MF primarily affects older adults, a stem cell transplantation is not a treatment option for most MF patients. For most people with MF, treatment remains aimed at controlling disease symptoms and complications, enhancing quality of life and extending survival.

Low-Risk MF Patients. For low-risk patients, treatment may include:

Asymptomatic Patients. Patients who are symptom-free (called "asymptomatic") and do not have signs of anemia, an enlarged spleen or other complications, are generally not treated. Some people remain stable and symptom-free for many years. However, these low-risk patients need to be monitored closely with regular medical checkups and examinations to detect any signs and symptoms of disease progression.

Symptomatic Patients. For low-risk patients with symptoms, treatment may include

- Ruxolitinib (Jakafi®), **or**
- Interferon alfa (Intron A, Roferon-A, Pegasys), although a situation in which these drugs are used may be best in the setting of a clinical trial

Intermediate-Risk and High-Risk MF Patients. For intermediate 1 risk (INT-1) patients, treatment may include:

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

For intermediate-2 risk (INT-2) and high-risk patients, doctors will determine on a case-by-case basis those who are candidates for allogeneic stem cell transplantation. For those eligible, the stem cell transplant may begin shortly after diagnosis.

Patients who are not candidates for allogeneic stem cell transplantation are encouraged to participate in clinical trials. Alternatively, patients can be managed with ruxolitinib to reduce symptoms and spleen.

Drug Therapies. Drug therapies used to treat MF patients include:

- Ruxolitinib (Jakafi®). Ruxolitinib is a prescription JAK1/JAK2 inhibitor that is available as a pill. JAK proteins send signals that affect the production of blood cells in the bone marrow. When JAKs send too many signals, they cause the body to make too many blood cells. Ruxolitinib works by inhibiting the JAK proteins and reducing its overactive signaling. It is FDA approved for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. The most common side effects are low platelet count, low red blood cell count, bruising, dizziness and headache. This oral drug is not associated with major toxicity and over time may slightly increase the risk of infectious complications such as pneumonia and urinary tract infections as well as shingles.
- Interferon alfa (Intron A, Roferon-A, Pegasys), given by subcutaneous injection, is a synthetic version of a substance made by cells in the body to fight infection and tumors. It has been used to treat enlarged spleen, bone pain and high platelet count in selected 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.

For specific drug information, see the free LLS publication *Understanding Side Effects of Drug Therapy,* the LLS list of drugs at www.LLS.org/drugs, and the Food and Drug Administration (FDA) drug information website at https://www.accessdata.fda.gov/scripts/cder/daf/.

Stem Cell Transplantation. Allogeneic stem cell transplantation is the only current treatment with the potential to cure MF, but it also carries a high risk of life-threatening side effects. In this procedure, the patient receives high doses of chemotherapy or radiation therapy to destroy the diseased bone marrow. Then, healthy blood-forming (hematopoietic) stem cells from a compatible donor (a related or unrelated person whose stem cells "match" the patient's) are infused into the patient. The transplanted healthy cells travel to the patient's bone marrow, replacing the defective stem cells. The new cells grow and provide a supply of red blood cells, white blood cells and platelets.

Allogeneic stem cell transplantation is usually risky for older patients and those individuals with other health problems. Therefore, allogeneic stem cell transplantation is recommended for younger patients with no other pre-existing health problems. However, allogeneic stem cell transplantation can be used in older people when 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 is a type of transplant that is being used to treat some patients with MF. Compared with standard allogeneic stem cell transplantation, reduced-intensity transplant delivers lower doses of chemotherapy drugs and/or radiation to the patient in preparation for the transplant. This approach may benefit older and sicker patients who are unable to tolerate high doses of chemotherapy drugs used in standard allogeneic stem cell transplantation.

Patients should talk with their doctors about whether stem cell transplantation is a treatment option for them. For additional information on stem cell transplantation, please see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Treatment Side Effects in MF. The side effects of treatment for MF will depend on many factors, including the type of treatment and dosage, the age of the patient and coexisting medical conditions. Therapy may induce fatigue, nausea, fever, chills, dizziness, shortness of breath, peripheral neuropathy (tingling, burning, numbness, or pain in the hands or feet), temporary loss of hair and other side effects.

Management of side effects is important. Patients should discuss any concerns about side effects with their doctor. Most side effects are temporary and resolve when treatment is completed. For specific drug information, see the free LLS booklet *Understanding Side Effects of Drug Therapy*.

Supportive Care in MF

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

Anemia. 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, vitamin B12 deficiency and folic acid deficiency. Blood transfusions are recommended for patients whose anemia 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 are based on the patient's serum erythropoietin (EPO) levels.

For patients with serum EPO levels lower than 500 mU/mL, treatment may include:

- Erythropoietin stimulating agents (darbepoetin alfa or epoetin alfa). Erythropoietin is a substance naturally produced by the kidneys that stimulates the bone marrow to produce red blood cells. Erythropoietin stimulating agents (ESAs) are made in the laboratory and they also work by stimulating the bone marrow to make red blood cells.

For patients with serum EPO levels at or higher than 500 mU/mL, treatment may include:

- Danazol or alternative androgens, synthetic versions of male hormones (androgens) that may help build up red blood cell production
- The immunomodulators (IMiDs) thalidomide (Thalomid®) and lenalidomide (Revlimid®), both given by mouth, which may help improve red blood cell counts. These drugs may be combined with prednisone, a steroid.

Enlarged Spleen (Splenomegaly). Many patients with MF have enlarged spleens 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. These include:

- Ruxolitinib (Jakafi®), a JAK inhibitor given by mouth that has been shown to reduce spleen size in some patients
- Hydroxyurea (Hydrea®), 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), a therapy that can also control spleen enlargement

- Surgical removal of the spleen (splenectomy), which may be considered if other forms of therapy have not reduced the pain or complications associated with an enlarged spleen. Benefits and risks 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 hemorrhaging, 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.

Thrombocytosis and Leukocytosis. Some MF patients suffer from thrombocytosis, which means their bone marrow produces too many platelets. Other MF patients suffer from leukocytosis, indicating that their bone marrow produces too many white blood cells. The chemotherapy drug, hydroxyurea (Hydrea®) may be given to reduce 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; in others, it may cause skin ulcers when taken over a long period.

Research and Clinical Trials for MF

Patients are encouraged to explore clinical trials and enter one if they are eligible. Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the FDA as standard treatments.

Clinical Trials. Every new drug or treatment regimen goes through a series of clinical trials before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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. Sometimes, a clinical trial is the best option for a patient.

For example, the discovery of the *JAK2* gene mutation in 2005 led to clinical trials of several JAK inhibitors in the treatment of MF. The *JAK2* mutation is one of several gene mutations believed to be involved in the development of MF. Combining JAK inhibitors with other agents, such as immunomodulatory drugs, androgens or inhibitors of pathways other than the JAK pathway, is also

being tested. These combination therapies may provide additional benefits, such as improving anemia or providing better and/or longer responses. Medications to improve anemia or decrease bone marrow fibrosis are being developed as well.

Drugs under investigation in clinical trials are included in the following list.

- JAK inhibitors now in clinical trials are showing effectiveness in reducing spleen size and symptoms such as night sweats and fatigue, and possibly improving anemia. These new treatments include pacritinib (SB1518) and NS-018.
- Histone deacetylase (HDAC) inhibitors play an important role in the regulation of gene expression. A clinical study of panobinostat (Farydak®, which is approved by the FDA for the treatment of multiple myeloma), in combination with ruxolitinib in patients with MF is ongoing. Pracinostat is another HDAC inhibitor that is being studied.
- Antifibrotic 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 MF. Lysyl oxidase (LOX) and lysyl oxidase-like (LOXL) are also antifibrotic medications being studied in a clinical trial.
- Imetelstat is a telomerase inhibitor, which affects the ability of dividing cells to repair the loss of DNA that happens during cell division. It is being studied in MF to improve bone marrow fibrosis, bone marrow function and blood cell counts.

Treatment Outcomes in MF

The prognosis (likely outcome of a disease) varies widely in patients with MF. Each patient's prognostic risk factors are evaluated individually.

Median survival for MF patients is approximately 15.4 years for low-risk patients, 6.5 years for INT (intermediate)-1risk patients, 2.9 years for INT-2 risk patients and 1.3 years for high-risk patients. Some people, however, may survive for decades following a diagnosis. It is important to know that outcome data can show how groups of people with MF responded to treatment, but data cannot always determine how any one person will respond. For these reasons, patients are advised to discuss survival information with their doctors.

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients to living cells and carries away the cells' waste products. It also contains immune cells to fight infections and platelets that can stop bleeding in damaged blood vessels.

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) that are 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 insulin and corticosteroids
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B12
- Electrolytes, such as calcium, potassium and sodium

Blood Cells. There are three types of blood cells suspended in the plasma.

- Red blood cells (the cells that carry oxygen)
  - Make up a little less than half of the body's total blood volume
  - Are filled with hemoglobin, a protein that picks up oxygen from the lungs and delivers it to the cells throughout the body. Hemoglobin then picks up carbon dioxide from the cells and delivers it to the lungs where it is removed when a person exhales.
- Platelets
  - Are fragments of cells (one-tenth the size of red blood cells)
  - Help stop bleeding from an injury. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the blood vessel, clump together and plug up the bleeding site with the help of blood-clotting proteins such as fibrin and electrolytes such as calcium.
- White blood cells (cells that fight infections). There are several types of white blood cells, including
  - Neutrophils. Immune cells that are a "phagocytes" (eating cells). They help fight infection by ingesting microorganisms and releasing enzymes that kill the microorganisms. A neutrophil is a type of granulocyte, a white blood cell that has small particles.
  - Eosinophils. Immune cells that have granules (small particles). They play an important role in the body's response to allergic reactions and infection with parasites.
  - Basophils. Immune cells that have granules (small particles). They play a role during allergic reactions and asthma.

- Monocytes. Immune cells that are also phagocytes. They can leave the bloodstream and enter tissues to attack invading organisms and fight off infection. They surround and kill microorganisms, ingest foreign material and remove dead cells.
- Lymphocytes. These white blood cells are found mostly in the lymph nodes, spleen and lymphatic channels. They are a key part of the immune system. There are three major types of lymphocytes. They are
  - T lymphocytes (T cells)
  - B lymphocytes (B cells)
  - Natural killer (NK) cells

New red blood cells, platelets and most white blood cells are formed in the bone marrow, a spongy tissue that is found in the central cavity of bones. The creation of new blood cells is controlled by the body's needs. The human body generates billions of new blood cells every day to replace old and worn out cells. Certain events also may prompt the body to produce additional blood cells. For example, the bone marrow will produce and release more white blood cells in response to an infection.

Although red blood cells, white blood cells and platelets vary in appearance and function, they all originate from a single type of unspecialized cell called a "hematopoietic stem cell." Hematopoietic, or blood-forming, stem cells are found in the bone marrow of the femurs (thigh bones), hips, vertebrae (back bones) and the ribs. An unspecialized hematopoietic stem cell can give rise to specialized cells that have specific functions. For example, a hematopoietic stem cell can give rise to a red blood cell that carries oxygen throughout the body, or it can give rise to a neutrophil, a type of white blood cell that helps fight infections. The process by which an immature cell becomes a mature cell with specific functions is called "differentiation."

The process of creating new blood cells through differentiation is called "hematopoiesis" (see Figure 1). When a stem cell divides, each "daughter" cell has the potential to either remain a stem cell or to become a specialized cell such as a red blood cell, a white blood cell or a platelet. For those cells "committed" to specialize, the stem cell generates an intermediate cell. The intermediate cell is called a "precursor" or "progenitor" cell. While the stem cell remains in an immature, unspecialized state, the progenitor cell divides and undergoes multiple stages of development, becoming more specialized at each stage, until it becomes a particular type of mature blood cell.

The hematopoietic stem cell can give rise to lymphoid stem cells and myeloid stem cells. The lymphoid stem cells create lymphoid progenitor cells. Different types of progenitor or precursor cells develop into different types of mature blood cells.

Through the process of differentiation, lymphoid progenitor or precursor cells can mature into T cells, B cells and NK (natural killer) cells.

Myeloid stem cells create myeloid progenitor cells. These precursor or progenitor cells will develop into mature blood cells including red blood cells, platelets and certain types of white blood cells (eosinophils, basophils, neutrophils and monocytes.) For example, a myeloid progenitor cell goes through various stages of development to become a neutrophil: myeloid progenitor → promyelocyte → myelocyte → metamyelocyte → band → neutrophil.

In healthy people, stem cells in the bone marrow produce new blood cells continuously. Once the blood cells have matured, they leave the bone marrow and enter the bloodstream.

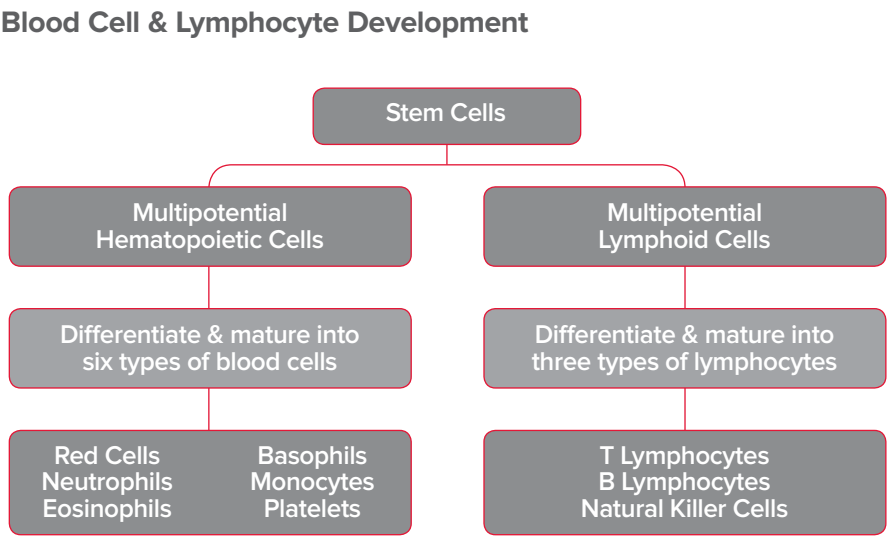

Figure 1. | **Stem cells** develop into blood cells (hematopoiesis) and lymphoid cells.

Health Terms

Acquired Mutation. Acquired (or somatic) mutation occurs at some time during a person's life and is present only in certain cells in the body; not inherited from a parent. The mutation can be caused by environmental factors or may be caused by a mistake during cell division.

Acute Myeloid Leukemia (AML). A rapidly progressing blood cancer that produces too many myeloblasts, which are immature myeloid cells.

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. For more information, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

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

Blast Cell. A young (or immature) blood cell.

Bone Marrow. Spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation.

Bone Marrow Aspiration. A test that extracts liquid bone marrow cells to examine for disease. A sample is usually taken from the patient's hip (pelvic) bone. After medication is given to numb the area, the liquid sample is removed using a special needle inserted through the hip bone into the bone marrow. Usually this test is done at the same time as a bone marrow biopsy.

Bone Marrow Biopsy. A test to examine marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip (pelvic) bone. After medication is given to numb the area, a special hollow biopsy needle is used to remove a core of bone containing marrow. Bone marrow aspiration and bone marrow biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together.

Cardiovascular Risk Factors. Factors that raise a person's risk of coronary heart disease and heart attack. Some 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, either by killing the cancer cells or by preventing them from dividing.

Chromosome. Threadlike structure within a cell that carries genes in a linear order. Human cells have 23 pairs of chromosomes: chromosome pairs 1 to 22, and pair 23, the sex chromosomes (XX for females and XY for males).

Chronic. A disease that persists or progresses over a long period of time.

Chronic Eosinophilic Leukemia (CEL). A disorder in which too many eosinophils (a type of white blood cell) are found in the bone marrow, blood and other tissues. Chronic eosinophilic leukemia may progress slowly over many years, or it may progress quickly to acute leukemia.

Chronic Myeloid Leukemia (CML). A slow-growing cancer in which too many myeloblasts are found in the blood and bone marrow. Myeloblasts are a type of immature white blood cell. Chronic myeloid leukemia may get worse over time as the number of myeloblasts increases in the blood and bone marrow. For more information, see the free LLS booklet *Chronic Myeloid Leukemia*.

Chronic Neutrophilic Leukemia (CNL). A disorder in which too many neutrophils (a type of white blood cell) are found in the blood. The additional neutrophils may cause the spleen and liver to become enlarged. Chronic neutrophilic leukemia may stay the same for many years or it may progress quickly to acute leukemia. For more information, see the free LLS factsheet *Chronic Neutrophilic Leukemia Facts*.

Clinical Trial. Carefully planned and monitored research study that tests how well new medical approaches work in patients. The goal of clinical trials for blood cancers is to develop new treatments for patients, improve their quality of life and increase their survival.

Clonal Disorder. A disorder that begins with one or more changes to the DNA of a single hematopoietic stem cell in the bone marrow.

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

Comprehensive Metabolic Panel. 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.

Constitutional Symptoms. Fatigue, weight loss, night sweats, and low-grade fever.

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

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

Deep Vein Thrombosis (DVT). The formation of a blood clot in a deep vein of the lower leg or pelvis.

DNA. Deoxyribonucleic acid. The genetic matter found in all cells. 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.

Embolism. See Pulmonary Embolism.

Eosinophil. A type of white blood cell that participates in allergic reactions and helps fight certain parasitic infections.

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 erythropoiesis-stimulating agents (ESAs).

Essential Thrombocythemia. A rare disorder 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 cell diseases.

Hematopathologist. A doctor who has special training in identifying diseases of the blood cells by examining blood, bone marrow, lymph, and body tissues under a microscope.

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 reduction 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). Protein on the surface of cells that helps the body distinguish its own cells from foreign cells. HLAs make up an individual's tissue type, which varies from person to person. HLA tests are done before a donor

stem cell transplant to determine if the tissues match between the donor and the person receiving the transplant.

Hypercellularity. An abnormal excess of cells, as in 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 exhibits 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 lactate dehydrogenase in the blood may be a sign of tissue damage and some types of cancer or other diseases.

Leukocyte. See White Blood Cell.

Leukocytosis. An increase in the total number of white blood cells.

Magnetic Resonance Imaging (MRI). A test that uses magnetic fields and radio waves to create images of the body's organs and tissues. It differs from a CT (computed tomography) scan in that the patient is not exposed to x-rays. Healthcare professionals use MRI to measure the size, or a change in size, of organs such as the lymph nodes, liver and spleen, or tumor masses.

Molecular testing. A test that looks for mutations in genes. DNA sequencing is a type of molecular test that checks for specific mutations in cells.

MRI. See Magnetic Resonance Imaging.

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 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 serious disorder 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. Myeloproliferative neoplasms usually become worse over time as the number of extra cells build up in the bone marrow and blood.

Neutropenia. A condition in which the number of neutrophils (a type of white blood cell) in the blood is below normal.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. The neutrophil is the main 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 disease by studying tissues 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 count different blood cells and to see whether the cells appear normal.

Phlebotomy. A procedure in which a needle is used to remove extra red blood cells from the blood.

Platelet. A small colorless tiny blood cell that helps control bleeding. Platelets are found in the blood and spleen. They help form blood clots to stop bleeding. Also known as "thrombocyte."

Plateletpheresis. A procedure during which blood is drawn and passed through a cell-separating machine that collects only the platelets. The remaining blood components are returned back to the body.

Polycythemia Vera (PV). A disorder in which the bone marrow produces too many red blood cells, causing the blood to abnormally thicken. White blood cells and platelets may also increase to well 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 be the result of 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 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 transplantation. In reduced-intensity stem cell transplantation (also called "nonmyeloablative stem cell transplantation"), patients receive lower doses of chemotherapy drugs and/or radiation to prepare for the transplant. This protocol may be safer than an allogeneic stem cell transplant, especially for older patients.

Refractory. A disease that does not respond to 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 Cell Mutation. A mutation that occurs at some time during a person's life and is present only in certain cells in the body. It is not inherited from a parent. The mutation may be caused by environmental factors or may be caused by a mistake during cell division.

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 in which the spleen is removed.

Splenomegaly. An enlarged spleen.

Stem Cell. A primitive cell from which other types of cells develop. In the bone marrow, blood-forming stem cells mature into red blood cells, white blood cells and platelets. Stem cells are found primarily in the bone marrow, but some leave the marrow and circulate in the bloodstream. 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, weakness on one side of the body, and problems talking, writing or understanding language.

Thrombocyte. See Platelet.

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

Thrombocytopenia. A condition characterized by 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. A thrombus is formed 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. Similar to an "embolism," a blood clot that travels from the site where it formed to another location in the body.

Transfusion. A procedure in which whole blood or certain elements of blood are injected into a patient's bloodstream.

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

Ultrasound. A procedure that uses high-energy sound waves to examine tissues and organs inside the body. The sound waves make echoes that form pictures of the tissues and organs on a computer screen.

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.

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. White blood cells are also called "leukocytes."

More Information

Free LLS publications include

Acute Myeloid Leukemia

Blood and Marrow Stem Cell Transplantation

Choosing a Blood Cancer Specialist or Treatment Center

Chronic Myeloid Leukemia

Chronic Neutrophilic Leukemia Facts

Myelodysplastic Syndromes

Understanding Clinical Trials for Blood Cancers

Understanding Lab and Imaging Tests

Understanding Side Effects of Drug Therapy

Visit "Suggested Reading" at www.LLS.org/suggestedreading to see a list of helpful books on a wide range of topics.

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