MYELOFIBROSIS: CHARTING THE COURSE FOR CARE

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WELCOMING REMARKS

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The Leukemia & Lymphoma Society

LEUKEMIA & LYMPHOMA SOCIETY

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Myelofibrosis

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An NCI-Designated Comprehensive Cancer Center

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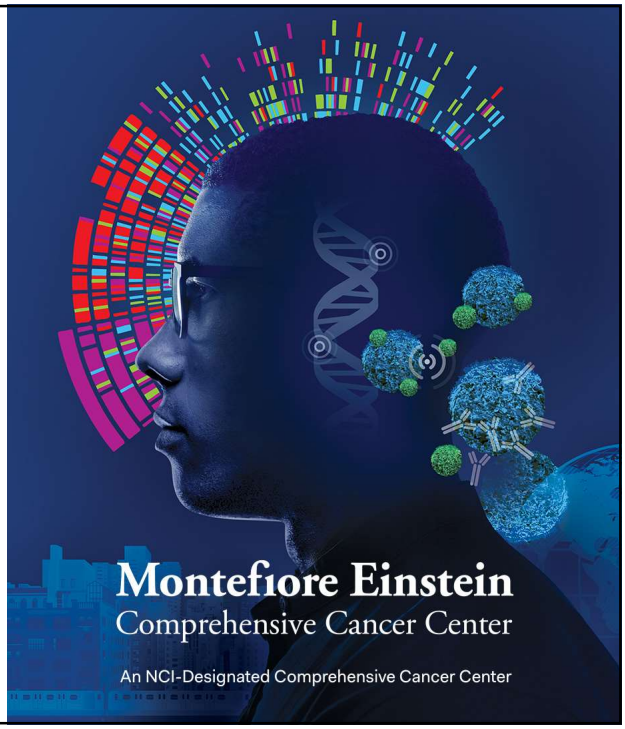

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What is myelofibrosis?

- Myelofibrosis(MF) is a rare Bone marrow disorder. Bone marrow is the spongy tissue inside the bone and the factory where our blood cells are produced.
- MF causes scarring of the bone marrow leading to abnormal production of blood cells
- As it becomes difficult for the scarred and stiff bone marrow to produce normal cells, blood cell production may move to the spleen (causing enlargement) or to other areas of the body

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Epidemiology

- Primary myelofibrosis is an uncommon disease, with an annual incidence of approximately 0.5-1.5 cases per 100,000 individuals in the United States.
- About 16 to 18 thousand people are living with Myelofibrosis in US.
- It can occur at any age but more common in people over 50 years of age

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Causation

- Myelofibrosis can be primary (without prior blood disease) or it can be secondary to blood diseases called Essential Thrombocythemia or Polycythemia Vera
- It is caused by changes in DNA called mutations. People with MF acquire these mutations at some point in their life and are not born with these mutations, nor do they pass this on to their children
- No obvious reason has been found as to why some people develop these mutations
- Exposure to industrial chemicals such as toluene and benzene and high levels of radiation can increase risk of MF

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Presentation

People with MF might not feel anything at all, disease could be diagnosed due to blood count abnormalities or enlarged spleen. They can also feel some or all of these symptoms mentioned.

- Pain in the upper left side of belly from enlarged spleen
- Feeling tired or weak which could be from low red blood cells (condition called anemia)
- Increased risk of infections due to low white blood cells
- Increased risk of bleeding or bruising due to low platelet cells
- Night sweats, fevers and weight loss due to inflammation caused by MF
- Early satiety or feeling full after eating small portions due to enlarged spleen

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Diagnosis

- MF is diagnosed based on set of criteria which include presentation, blood tests, physical exam, imaging and test called Bone marrow biopsy
- Blood tests include complete blood counts, LDH and testing for mutations(alterations) in genes especially JAK2, CALR and MPL.
- These 3 gene mutations are usually mutually exclusive, that is if one of these genes is mutated, the other 2 genes will not be mutated. These are often also called driver mutations meaning that these drive the disease process. About 5-10% of MF is caused by mutations in genes other than these 3 genes.

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Janus Kinase (JAK)

- Janus is the Roman god of all beginnings, gates, transitions, time, choices, duality, doorways, passages, and endings.
- Janus Kinase is the gene which is most commonly mutated in MF.
- A slight change in the gene called JAK2V617F mutation is responsible for about 60% of MF cases.

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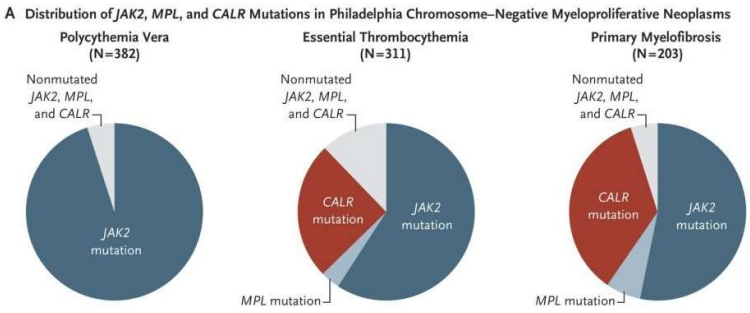
CALRETICULIN

Somatic *CALR* Mutations in Myeloproliferative Neoplasms with Nonmutated *JAK2*
Nangalia et al. NEJM Dec 2013

Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms
Klampfl et al. NEJM Dec 2013

- Most patients with ET or MF, not associated with a *JAK2* or *MPL* alteration, carried a somatic mutation in *CALR*



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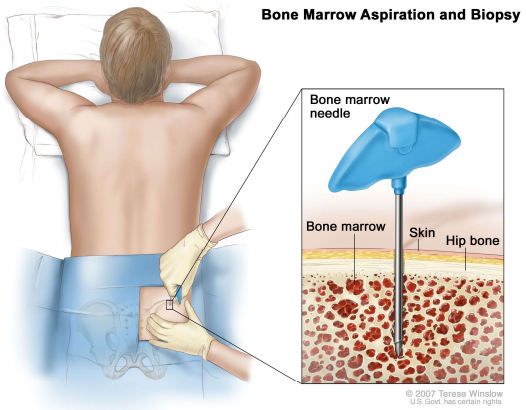
Bone marrow biopsy

Procedure done to take fluid and tissue from the hip bone.
Usually, skin and bone is numbed by local anesthesia like Lidocaine and needle is inserted to take bone marrow fluid and tissue.
Sometimes, the procedure can also be done under X ray or CT scan guidance under light sedation (light sleep).
This test gives important information about the disease which helps in the diagnosis, prognosis and treatment strategies.



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Additional testing

- Imaging tests like ultrasound, CT scan and MRI abdomen to evaluate spleen size and other organs like liver
- Cytogenetic analysis to look for abnormal changes in the chromosomes of the cancer cells. Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. In some cases of MF, the chromosomes of the cancer cells have abnormal changes that can be seen under a microscope, such as extra or missing chromosomes, or broken or rearranged chromosomes.
- DNA sequencing to examine the exact sequence (order) of DNA. By comparing the sequence of DNA in cancer cells with the DNA in normal cells, genetic changes that are unique to the cancer cells can be found,

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Myelofibrosis Symptom Assessment

Circle the one number that describes how, during the past Week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with sexual desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your overall quality of life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

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Prognosis

There are different scoring systems like DIPSS, DIPSS plus, MIPSS which doctors use to predict MF disease severity and prognosis.

These scoring systems take your age, blood work, bone marrow findings among other things into account.

People can be in different risk categories like low, intermediate and high risk based on these findings.

Approximate life expectancy can vary from 15.4 years for low risk individuals to 1.3 years for high risk.

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Complications

- Acute Myeloid Leukemia: about 15 to 20% of people with MF can transition to acute leukemia
- Portal Hypertension: Increased blood flow from an enlarged spleen can lead to high blood pressure in the portal vein (portal hypertension). This in turn can force excess blood into smaller veins in your stomach and esophagus, potentially causing these veins to rupture and bleed.
- Extramedullary hematopoiesis: Formation of blood cells outside the bone marrow can cause lumps or enlargement in organs like spleen and liver
- Increase risk of severe infections and bleeding due to decreased white blood cells and platelets

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Treatment for low-risk disease

- Many patients with low risk disease can be monitored without treatment
- Sometimes supportive treatment like red blood cells or erythropoietin stimulating agents are used to increase red blood cells in anemia
- JAK inhibitors can be used in patients feeling symptoms related to splenomegaly and constitutional symptoms from Myelofibrosis
- Clinical trial participation when available

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Treatment for intermediate-risk disease

- Many individuals with intermediate risk disease are candidates for JAK inhibitor therapy. There are currently 4 FDA approved JAK inhibitors: Ruxolitinib, Fedratinib, Pacritinib and Momelotinib. There are additional JAK inhibitors in clinical trials.
- Individuals are also considered for Allogenic stem cell transplant which is the only curative option at this time.
- Clinical trial participation is always encouraged whenever possible

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Treatment for high-risk disease

- Bone marrow transplant is the preferred treatment but it is a high risk procedure and not considered safe for older people or people with other high risk health conditions
- Jak inhibitor therapy is also used in many patients with high risk disease.
- Clinical trials when possible
- Intravenous or oral chemotherapy drugs similar to the ones used in acute leukemia or other condition called myelodysplastic syndromes

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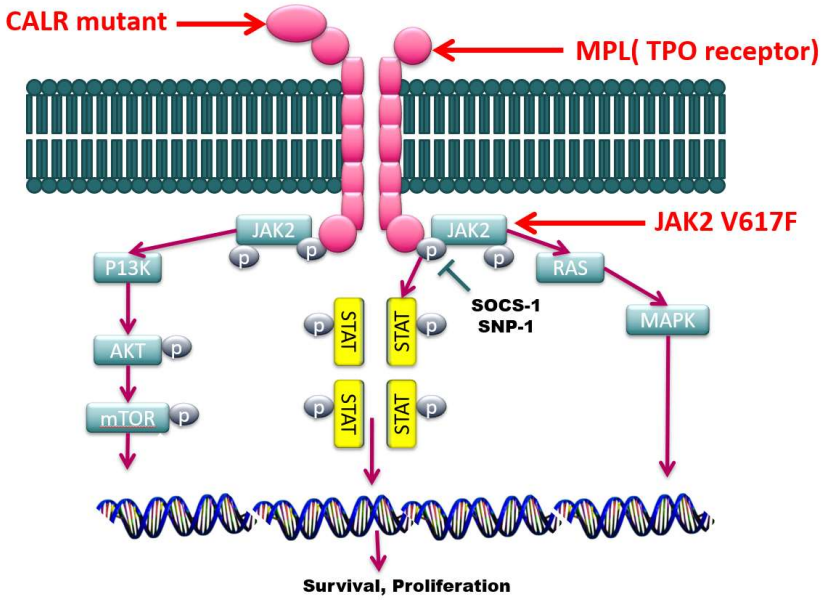
JAK signalling - Hyperactive



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Jak inhibitors

- JAK-STAT signaling pathway is instrumental in causing this disease
- Inhibiting JAK leads to decrease in spleen size and the inflammation related symptoms
- JAK is needed for normal blood cell production, thus inhibiting JAK can also lead to decrease blood cells
- JAK inhibitors do not cure Myelofibrosis, they help in managing disease symptoms and spleen size
- 4 JAK inhibitors are currently approved by FDA

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Jak inhibitor: Ruxolitinib

- Brand name : Jakafi®
- First JAK inhibitor approved for use
- Decreased spleen size and symptoms
- Can cause decrease in blood counts
- Available in different dosages from 5 mg twice daily to 25 mg twice daily
- Dose is dependent on baseline blood counts
- Individuals can gain weight on this drug

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COMFORT Trial

- Ruxolitinib: JAK-1 and 2 inhibitor used in randomized trial in symptomatic MF patients
- At 24 weeks, 42% patients had decrease in spleen size compared to 0.7% in placebo
- 46 % had symptom reduction
- Responses irrespective of JAK mutation status
- Main adverse event: Decreased cell counts
- Led to the FDA approval in Nov 2011 in symptomatic patients with intermediate to high risk MF

Verstovsek et al. NEJM 2012

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Jak Inhibitor: Fedratinib

- Brand name: Inrebic®
- Approved for adult patients with intermediate-2 or high-risk myelofibrosis (MF) who have platelet counts ≥50K/μL.
- Black Box warning for a very small risk for Wernicke's encephalopathy. Patients are checked for Vitamin B1 deficiency and treated with Vitamin B1 to avoid this rare complication
- Nausea, vomiting and diarrhea can happen which can be easily treated
- Dose is 400 mg once daily

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Jak inhibitor: Pacritinib

- Brand name: Vonjo®
- Approved for intermediate or high-risk primary or secondary myelofibrosis and who have platelet (blood clotting cells) levels below 50K/μL.
- Common side effects include diarrhea, low blood counts, nausea, bleeding and peripheral edema.
- Dose is 200 mg twice daily

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Jak inhibitor: Momelotinib

- Brand name: OJJAARA
- Approved for treatment of intermediate or high-risk myelofibrosis with anemia(low red blood count or hemoglobin).
- Increased risk of infections, low blood counts, liver toxicity, nausea, diarrhea
- Dose is 200 mg orally once daily

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Toxicity of Jak inhibitors

- Decreased blood counts as Jak signaling is essential for hematopoiesis(normal blood cell production)
- Infections like zoster, TB reactivation
- Small increased risk of other malignancies
- Major risk of cytokine storm, rebound splenomegaly with abrupt cessation of Jak inhibitor in myelofibrosis. Recommendation is to either switch to alternate Jak inhibitor or taper slowly with steroids and close monitoring

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Clinical trials

- Clinical trial participation is always encouraged
- Many clinical trials are very promising
- Different inhibitors other than JAK inhibitors are in development for use by themselves or in conjunction with JAK inhibitors
- Antibodies/ vaccines against JAK and CALR are also being developed
- Find the clinical trials available to you in myelofibrosis, please use the website: clinicaltrials.gov. https://clinicaltrials.gov/search?cond=Myelofibrosis

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Bone marrow transplant

- Allogeneic stem cell transplantation is the only curative treatment for this disease. This involves the use of stem cells from someone other than the patient. The donated stem cells can come from either a person related or not related to the patient.
- Before beginning an allogenic SCT, the patient receives a conditioning treatment that consists of either chemotherapy or radiation or both.
- Infections, stem cell rejection and graft versus host disease are some of the complications of the transplant
- Candidates for this procedure are carefully chosen by a team of doctors as the procedure can be very risky

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Supportive Care

- Diet: Healthy diet rich in fruits, vegetables, whole grains, fish, oils, and nuts is recommended.
- Physical activity: discussion with doctor and as well tolerated
- Rest: Adequate rest and sleep to manage fatigue
- Decrease infection risk: Hand washing, staying current on vaccines, avoid sick contacts, wearing face masks in certain situations
- Mental Health and Emotional Support

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Resources

- https://www.LLS.org/MPN
- https://www.mpnresearchfoundation.org/patient-caregiver-resources
- Patient support groups: local, internet and social media
- Resources at cancer centers

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LLS EDUCATION & SUPPORT RESOURCES

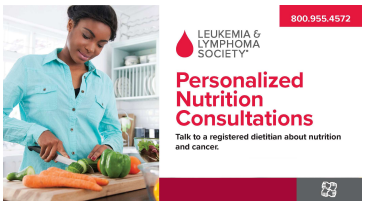
HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: www.LLS.org/ContactUs
All email messages are answered within one business day.



NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.llsnutriton.org

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation

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LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, **moderated by oncology social workers**. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**

Education Videos

Community of blood cancer patients, survivors and caregivers supporting each other and giving trusted information and resources, please visit **www.LLS.org/EducationVideos**

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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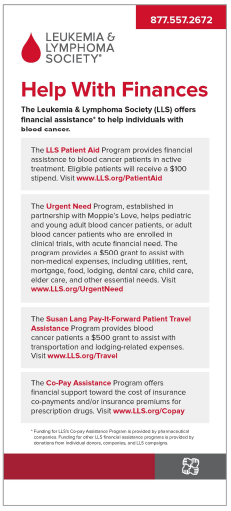
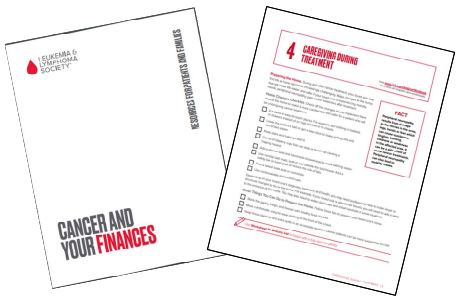


The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: **www.LLS.org/Finances**



To order free materials: **www.LLS.org/Booklets**

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THANK YOU
Please fill out Program Evaluation at
LLS.org/MF_eval
We have one goal: A world without cancers
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