

# Polycythemia

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many slide were adapted from Dr Mansor Al-Jabry

# Learning Objectives

- To understand the meaning of **myeloproliferative neoplasm (MPN)** and its clinical presentation.
- To differentiate between **primary and secondary polycythemia**.
- To obtain an overview of **primary myelofibrosis** and **essential thrombocythemia**.
- To appreciate the importance of **genetic abnormalities (clonality)** in these neoplasms and the idea of **targeted therapy**.


 Kingdom of Saudi Arabia  
 Ministry of Health  
 Tall - Directorate of Health Affairs  
 King Fahd Medical Complex  
 Laboratory and Blood Bank

Medical Record Number: 3180113231  
 Name: Ghulam Rasool Ansari  
 Age: 31 Year/Mon/Days  
 Nationality: India  
 Consultant in Charge: \_\_\_\_\_  
 Room/Bed No: \_\_\_\_\_  
 Dept/Unit: \_\_\_\_\_

### Therapeutic Phlebotomy

- Incomplete request will not be accepted by Blood Bank.
- Venesection will be done only at the written request from the Patient's physician.
- Therapeutic Phlebotomy time: Sunday to Thursday: Timing: 8:30 a.m. to 2:00 p.m.
- Therapeutic Phlebotomy will be done during 2 days from the date of investigation.

History of Smoking: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Diabetes Mellitus Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	IHD: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Asthma/Allergy Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Investigations: Hb: 20.2	HGT: 59.3	RBG Count: 7.00	PLT: 271
Clinical Diagnosis: Polycythemia (H7)			
Vitals: B.P. 130/80	Pulse 80	Temp 36.8	Fitness for Venesection Fit <input checked="" type="checkbox"/> Unfit <input type="checkbox"/>
Amount of whole Blood To Be Withdrawn: 400 ml Frequency: _____			

**Please Note:** If your Patient has any of the following and if phlebotomy is requested and believed to be indicated/essential. The Treating Doctor is required to attend the entire procedure.

- Heart Disease
- IHD/Unstable Angina
- MI in recent Past
- Severe Hypertension
- Respiratory Disease
- Asthma/O<sub>2</sub>
- COPD
- Resp distress/Emphysema
- Physically/Mentally Challenged
- CVA /Stroke
- Seizures
- Others

**Consent of the patient to withdraw above mentioned amount of blood:**

Patient Name: اسم المريض: ج. راسول انصاري  
 Signature (التوقيع): ج. راسول انصاري

I have Discussed the advantages and Adverse effects of Therapeutic phlebotomy with the patient and request that above mentioned amount of Blood to be withdrawn from the patient. He/she has no medical contraindications for this procedure.

Ordering Physician Name: \_\_\_\_\_  
 Department: \_\_\_\_\_  
 Signature: \_\_\_\_\_  
 Date: DR. SHAIKH ARMED ALI ER RESIDENT 12-11-16.

### For KFH Blood Bank Use

Polycythemia No.	Date:	Time:			
H/O Food within last 4 hrs Yes <input type="checkbox"/> No <input type="checkbox"/>	Vitals	B.P	Pulse	Temp	Wight
H/O Last Phlebotomy	Name of B.B. Physician:		Stamp & Sig.		

## Table 1. WHO classification of myeloid neoplasms and acute leukemia **WHO Updated 2016**

### WHO myeloid neoplasm and acute leukemia classification

#### **Myeloproliferative neoplasms (MPN)**

Chronic myeloid leukemia (CML), *BCR-ABL 1*<sup>+</sup>

Chronic neutrophilic leukemia (CNL)

Polycythemia vera (PV)

Primary myelofibrosis (PMF)

PMF, prefibrotic/early stage

PMF, overt fibrotic stage

Essential thrombocythemia (ET)

Chronic eosinophilic leukemia, not otherwise specified (NOS)

MPN, unclassifiable

#### **Mastocytosis**

#### **Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2***

## MPN features

- **Cytosis.**
- **Organomegaly (mainly splenomegaly).**
- **High uric acid.**
- **Hypercellular bone marrow.**
- **Clonal evolution.**
- **Progression to acute leukaemia (mainly AML).**

**Table 1.** Classification of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

**1. Myeloproliferative neoplasms (MPN)**

- 1.1. Chronic myelogenous leukemia, *BCR-ABL1*-positive (CML)
- 1.2. Polycythemia vera (PV)
- 1.3. Essential thrombocythemia (ET)
- 1.4. Primary myelofibrosis (PMF)
- 1.5. Chronic neutrophilic leukemia (CNL)
- 1.6. Chronic eosinophilic leukemia (CEL)
  
- 1.7. Mast cell disease (MCD)
- 1.8. MPN, unclassifiable

**BCR-ABL must be negative**

**2. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1***

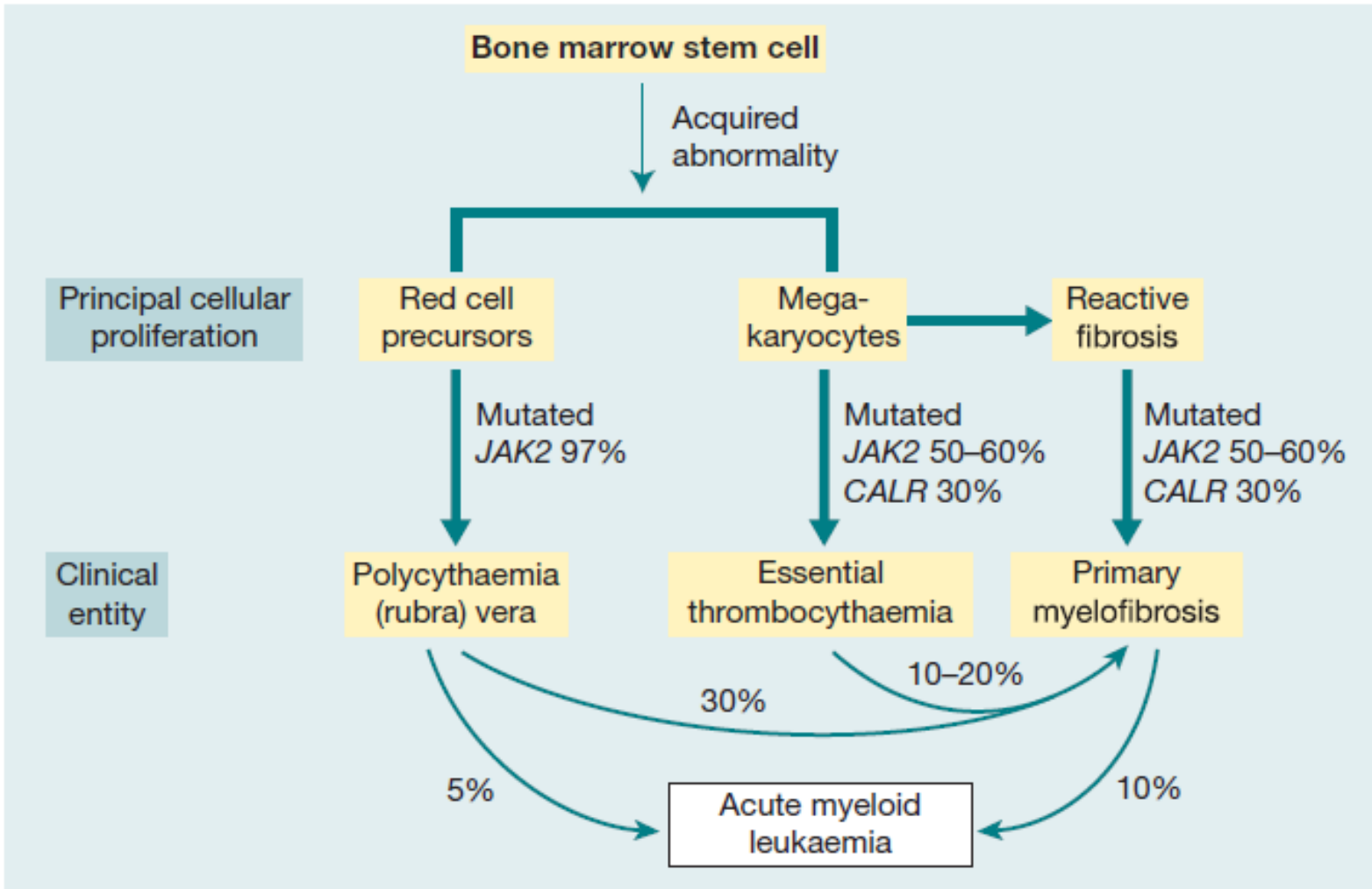
**3. MDS/MPN**

- 3.1. Chronic myelomonocytic leukemia (CMML)
- 3.2. Juvenile myelomonocytic leukemia (JMML)
- 3.3. Atypical chronic myeloid leukemia, *BCR-ABL*-negative (aCML)
- 3.4. MDS/MPN, unclassifiable

**4. Myelodysplastic syndromes (MDS)**

**5. Acute myeloid leukemia (AML)**

For reading

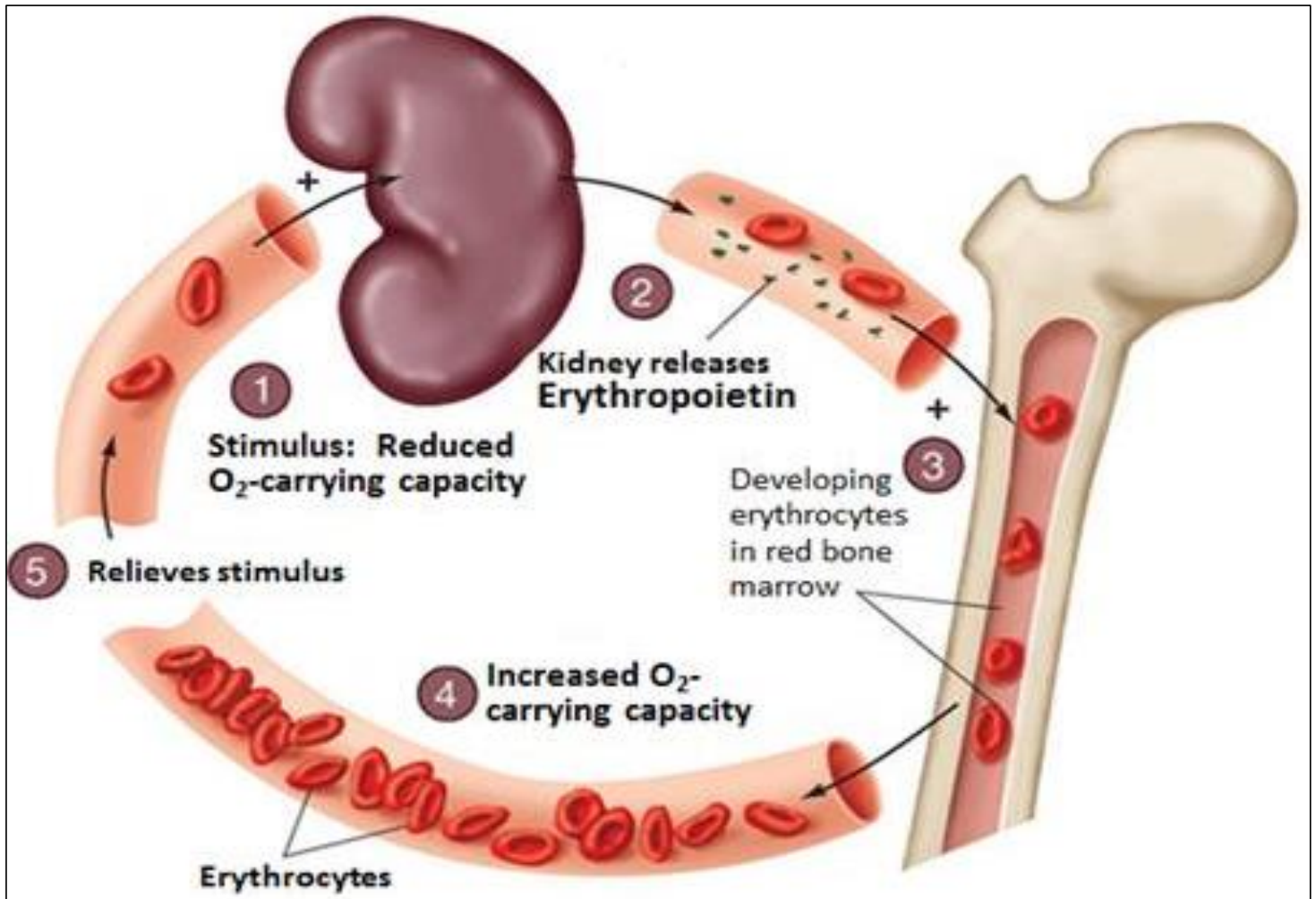


# Polycythemia

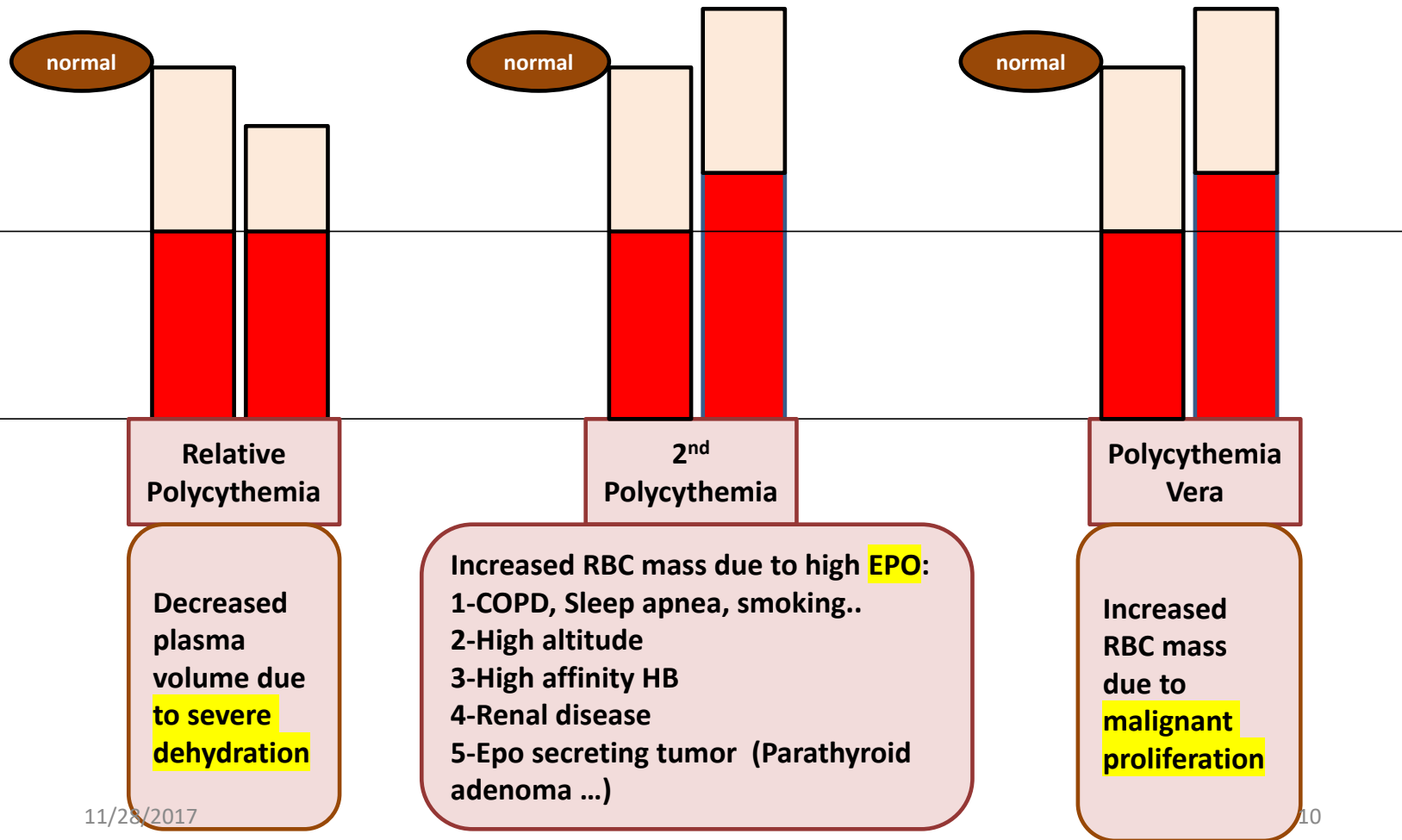
- In Greek, “too many cells in the blood.”
- Absolute increase in total body red cell volume (or mass).
- Manifests itself as a **raised hemoglobin** or packed cell volume (PCV), **maybe masked** by other disorders like iron deficiency.
- Almost always, accompanied with **JAK2 mutation**.



# Regulation of Erythropoiesis

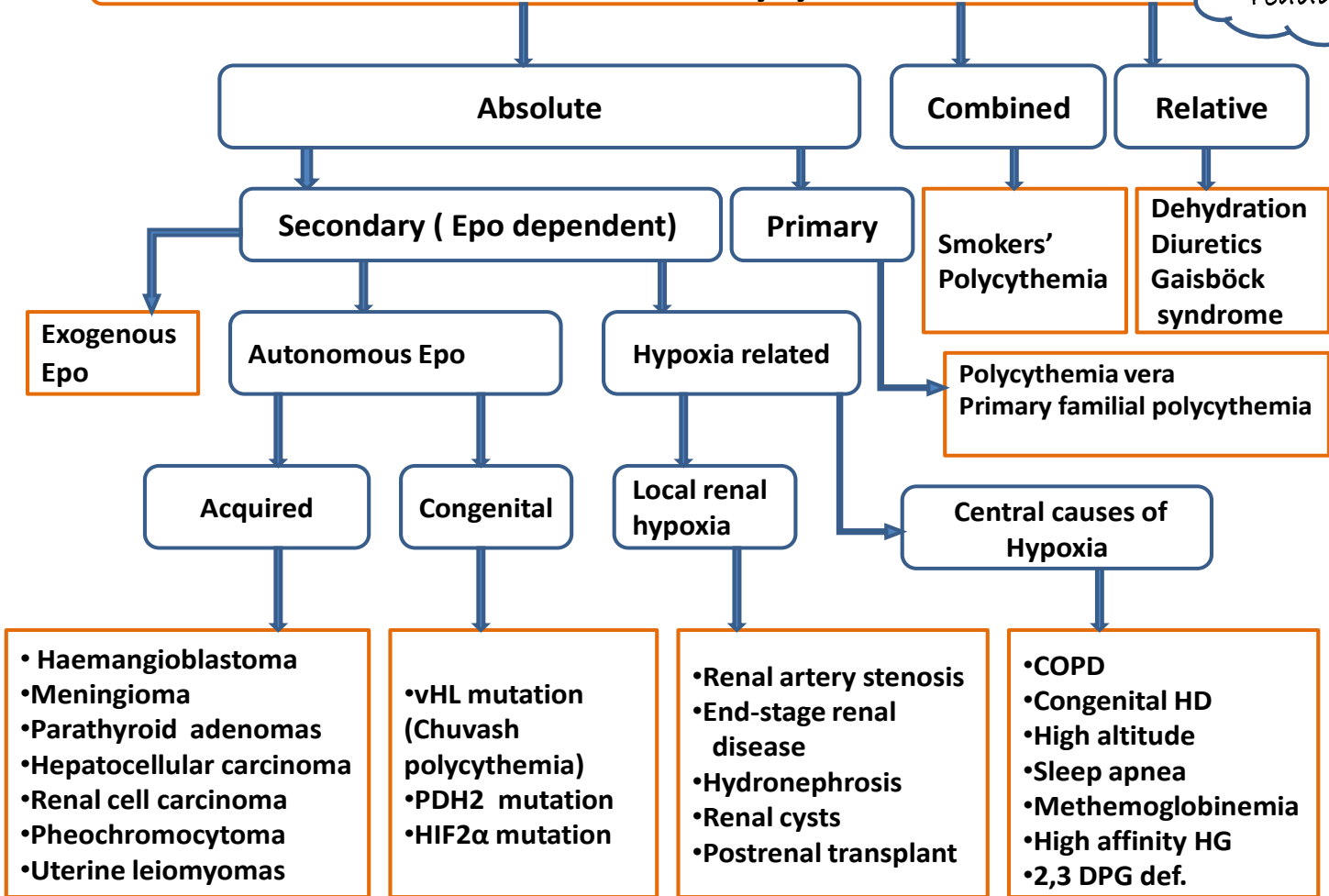


# Classification of Polycythemia



# Classification of Polycythemia

For reading



# Polycythemia Vera

• It is a type of MPN characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis (intrinsic proliferation and anti-apoptotic).

## Diagnostic Features:

- HB >16.5g/dl in men, 16.0g/dl in women.
- Hypercellular bone marrow (pan-myelosis).
- JAK2 mutation in >95% of cases
- No increase in serum erythropoietin level

# Polycythemia Vera

For  
reading

Table 4. WHO criteria for PV

## WHO PV criteria

Updated  
WHO 2016

### Major criteria

1. Hemoglobin  $>16.5$  g/dL in men

Hemoglobin  $>16.0$  g/dL in women

or,

Hematocrit  $>49\%$  in men

Hematocrit  $>48\%$  in women

or,

increased red cell mass (RCM)\*

2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3. Presence of *JAK2V617F* or *JAK2* exon 12 mutation

### Minor criterion

Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

\*More than 25% above mean normal predicted value.

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels  $>18.5$  g/dL in men (hematocrit, 55.5%) or  $>16.5$  g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

# Clinical features of PV

## 1-Increased blood viscosity

- Hypertension, pruritus.
- Headache, dizziness, visual disturbances & paresthesia.

## 2- Thrombosis

- Deep vein thrombosis
- Myocardial infarction
- Mesenteric, portal or splenic vein thrombosis

3-Splenomegaly in 70%

4-Hepatomegaly in 40%

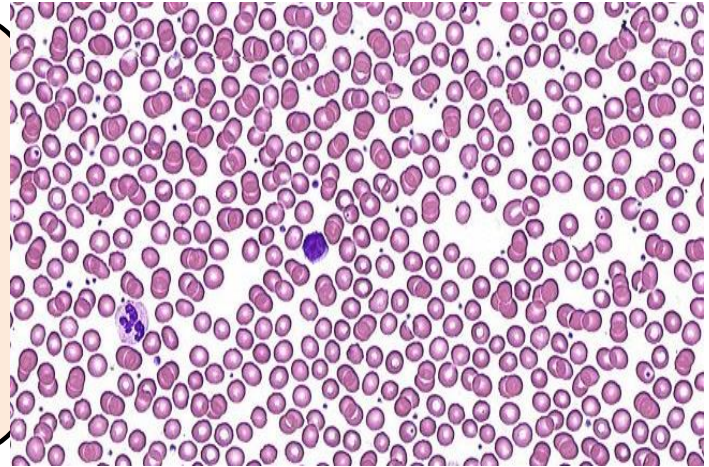
# Investigations

## CBC:

- \*RBC: increased
- \*Hb: increased
- \*WBC & PLT :mildly increased (usually).

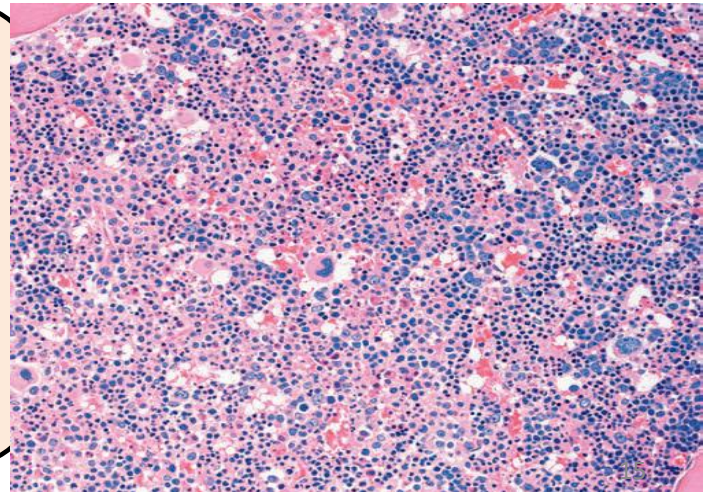
## Blood smear:

- Excess of normocytic normochromic RBC.
- ± Leukocytosis & thrombocytosis.



## Bone marrow

- Hypercellular.
- Predominant erythroid precursors.
- ± Increased megakaryocytes & myeloid precursors.



↑ Blasts → AL transformation

# Complication & treatment

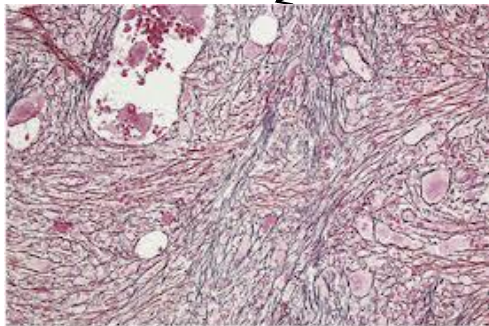
## Diagnosis of Polycythemia Vera

### Treatment:

- Venesection + Aspirin
- ± Myelo-suppressive drugs (hydroxyurea)

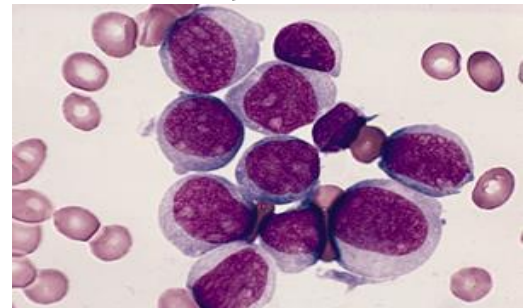
10-15 years

20-30%



Myelofibrosis

5-10%



Acute leukemia



**Bone marrow stem cell**

↓ Acquired abnormality

Principal cellular proliferation

Red cell precursors

Mega-karyocytes

Reactive fibrosis

Mutated *JAK2* 97%

Mutated *JAK2* 50–60%  
*CALR* 30%

Mutated *JAK2* 50–60%  
*CALR* 30%

Clinical entity

Polycythaemia (rubra) vera

Essential thrombocythaemia

Primary myelofibrosis

30%

10–20%

5%

Acute myeloid leukaemia

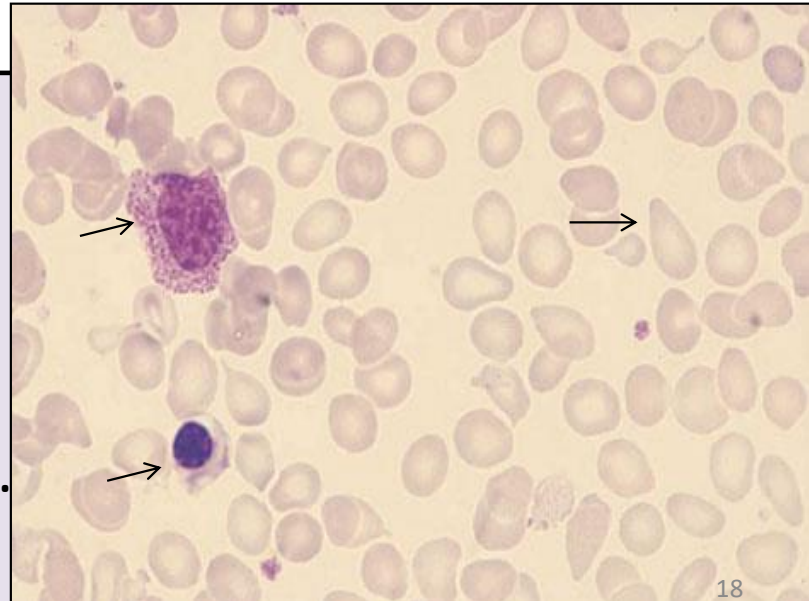
10%

# Primary Myelofibrosis

- It is a clonal MPN characterized by a proliferation of megakaryocytes & granulocytes in the bone marrow that associated with deposition of fibrous connective tissue and extramedullary haematopoiesis.

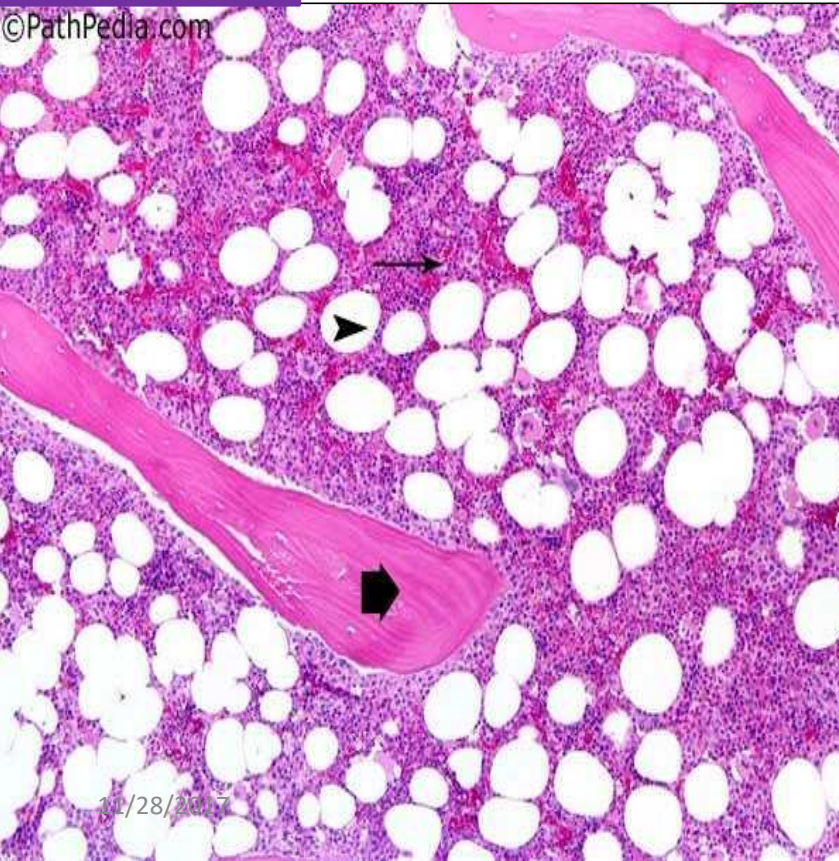
## Clinical features

- Anemia
- Leukoerythroblastic blood picture.
- Massive splenomegaly.
- Fibrotic bone marrow.
- JAK2 mutation (50%-60%).
- Risk of AML transformation (10-20%).

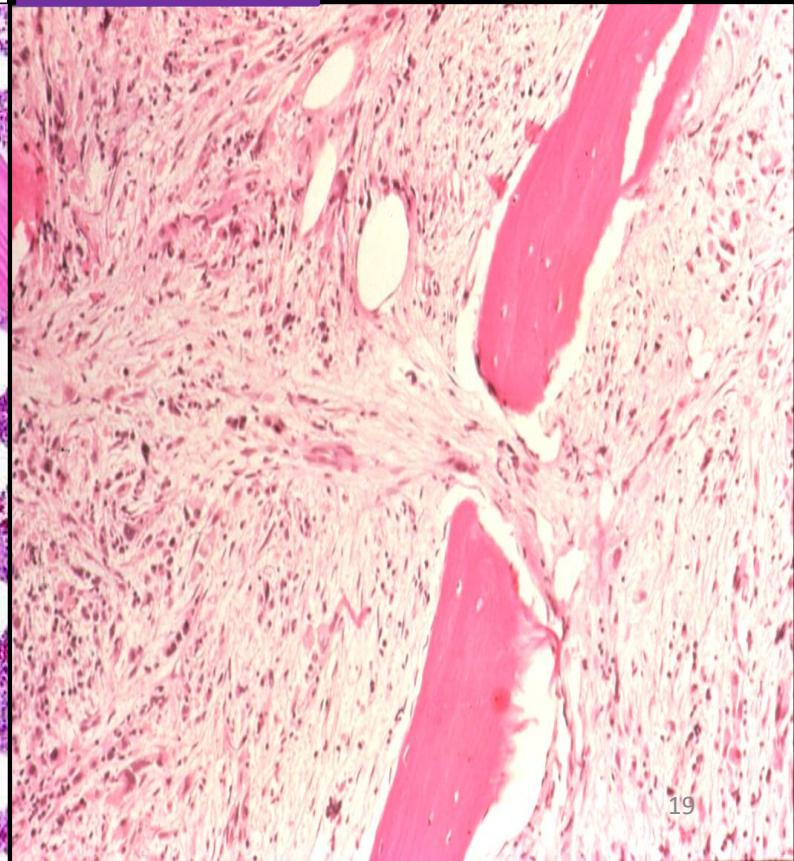


# Bone marrow in Myelofibrosis

Normal BM



Fibrotic BM



# Stages of PMF

Pre-fibrotic stage

Proliferation of megakaryocytes & granulocytes

- Leukocytosis  
- Thrombocytosis

7-10 years survival

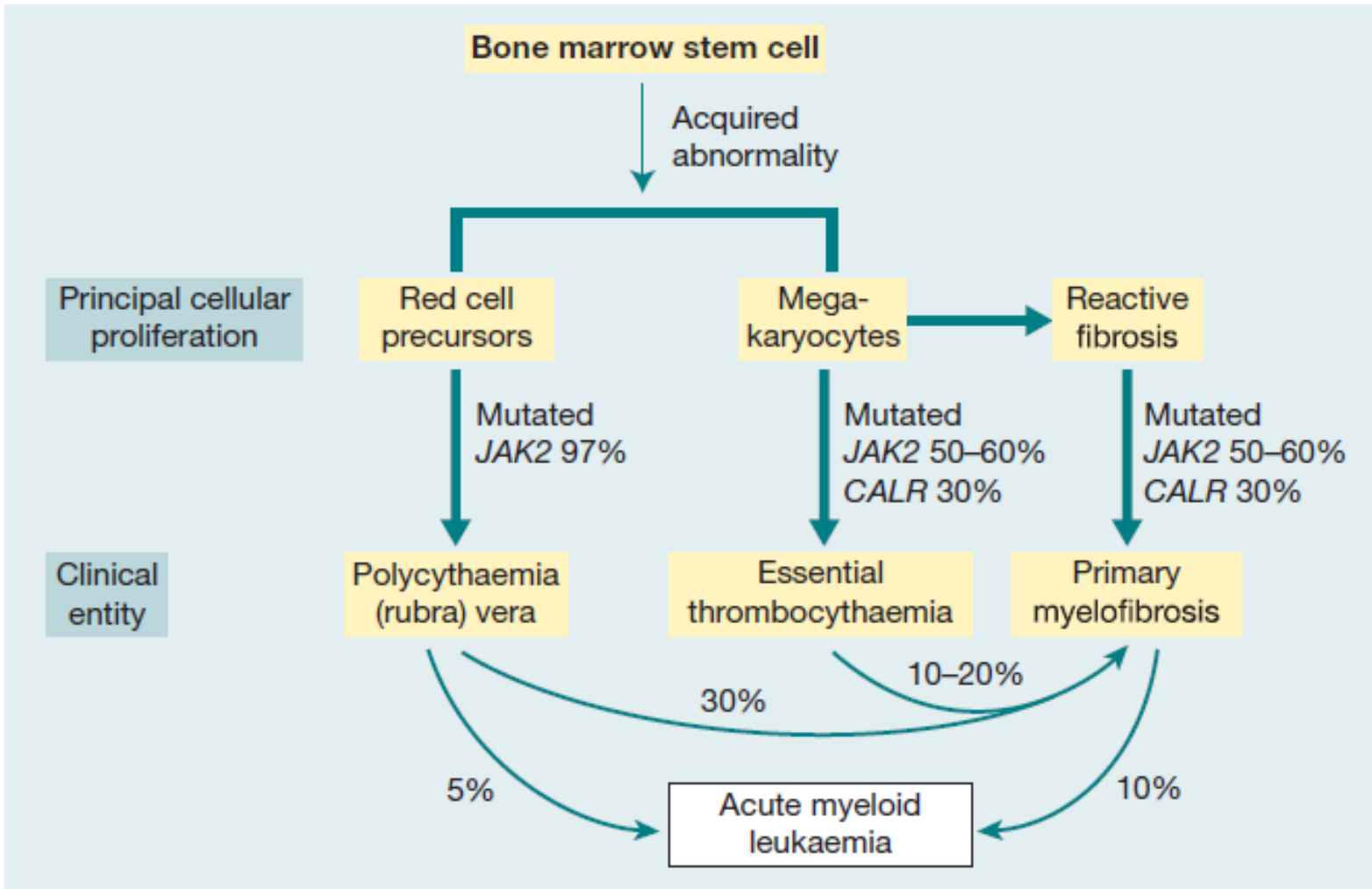
Fibrotic stage

Anemia  
Leukopenia  
Thrombocytopenia  
Extramedullary hematopoiesis

3-7 years survival

AML transformation

≤1 year survival



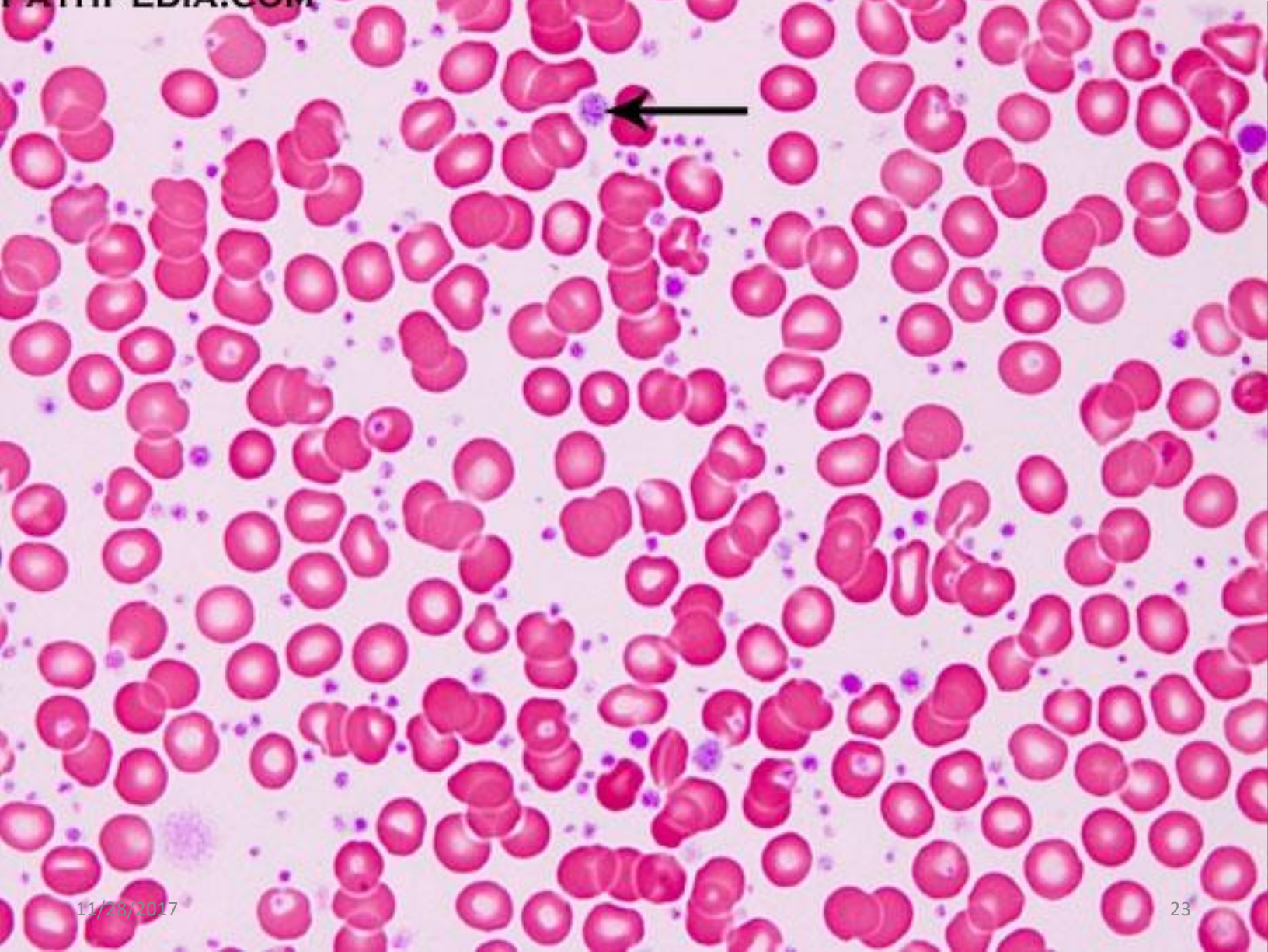
# Essential Thrombocythemia

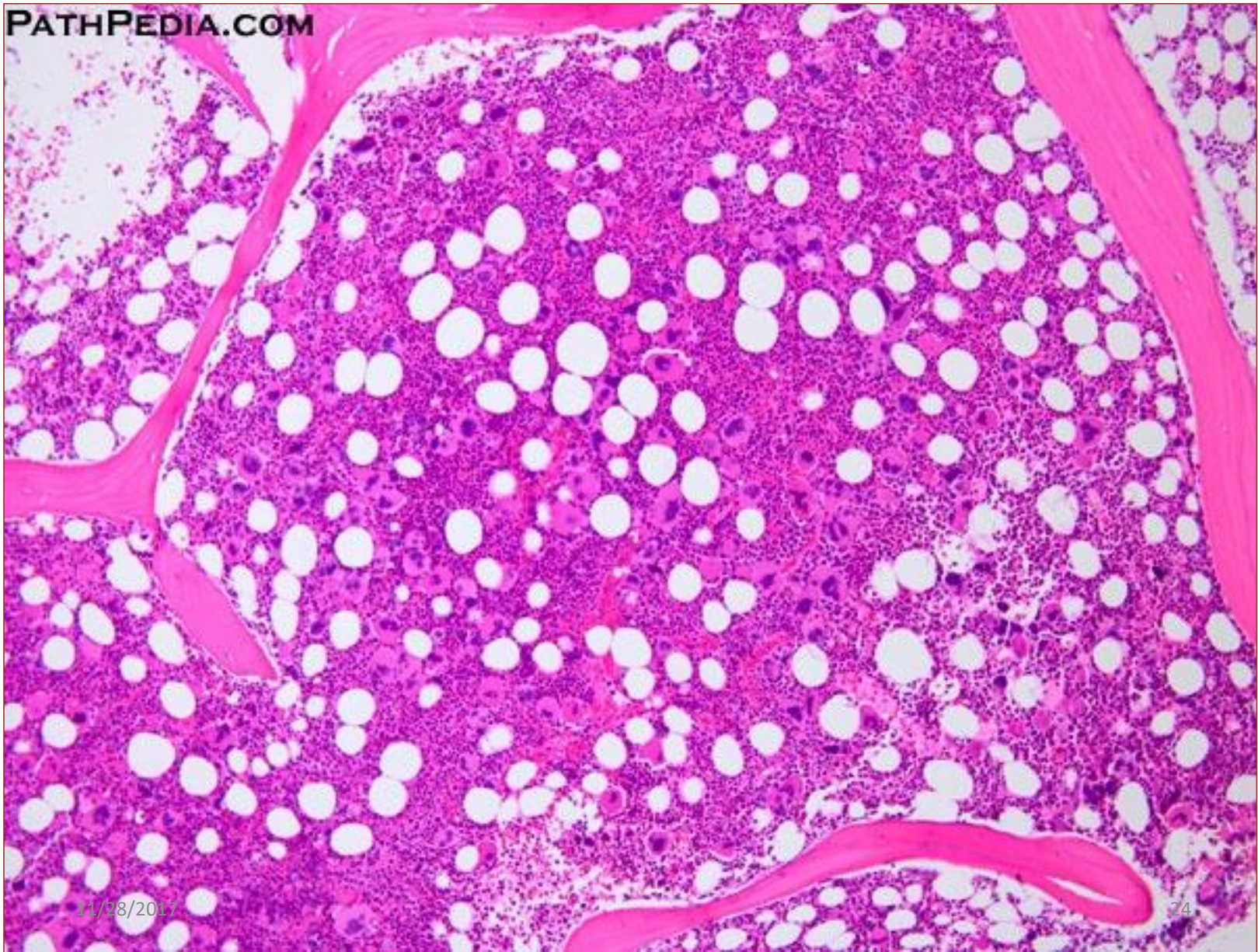
- It is a MPN that involves primarily the megakaryocytic lineage and characterized by sustained thrombocytosis .

## Diagnostic Features

- Sustained thrombocytosis  $\geq 450 \times 10^9/L$ .
- Hypercellular BM with megakaryocytic proliferation.
- Exclusion of: CML, MDS, PV & PMF.
- JAK2 V617F mutation (50-60%), CARL or MPL mutations If negative; no evidence of reactive thrombocytosis:

Iron def. ,splenectomy, surgery, infection ,autoimmune disease....







# Essential Thrombocythemia

## Clinical Presentation

- Asymptomatic (50%)
- Thrombosis
- Bleeding
- Mild splenomegaly (50%)
- Mild hepatomegaly (20%)

Very indolent  
(5% risk of AML transformation)

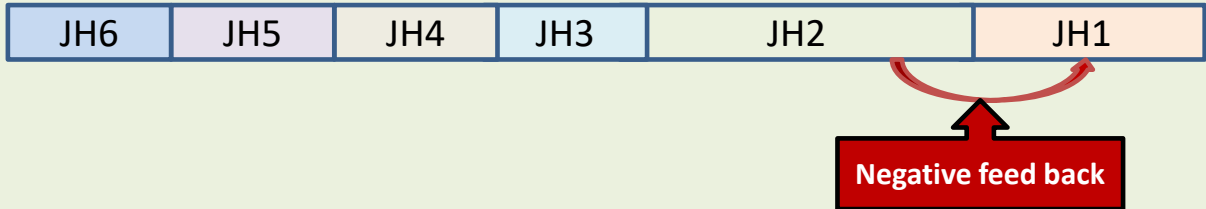
## Treatment

Aspirin ± Hydroxyurea

# JAK2 Mutation

- **JAK2: (Ch 9p with 26 exons), a non-receptor protein tyrosine kinase involved in signal transduction pathway.**

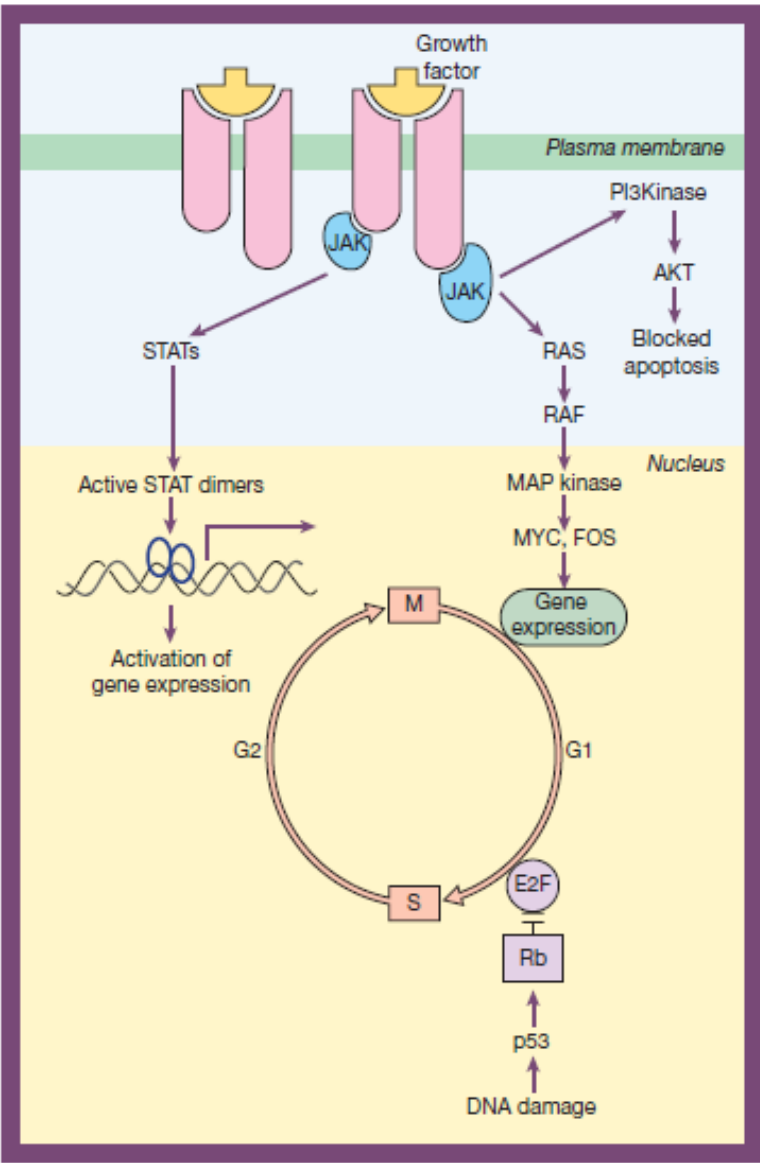
JAK2 kinase domains structure

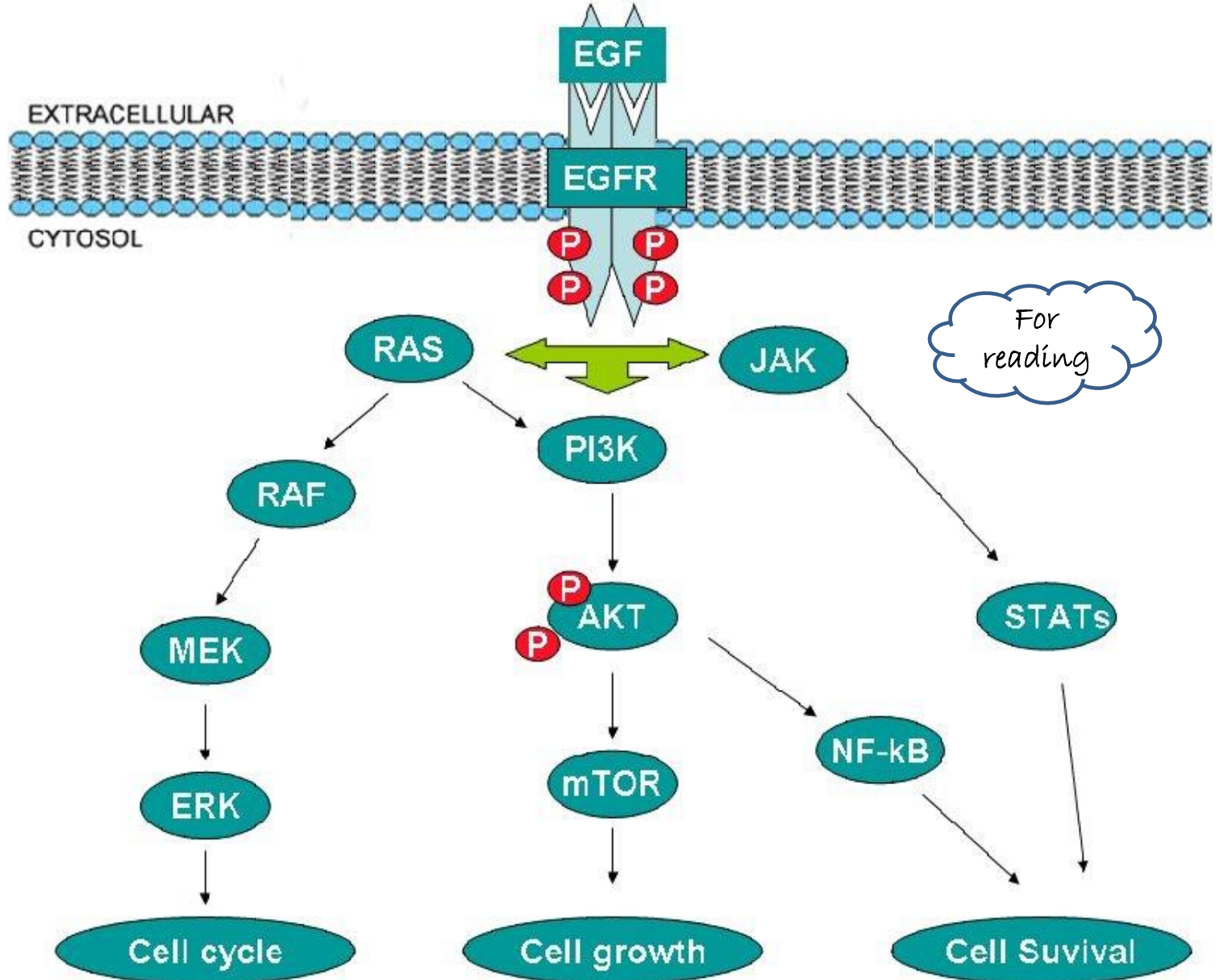


## JAK2 mutation :

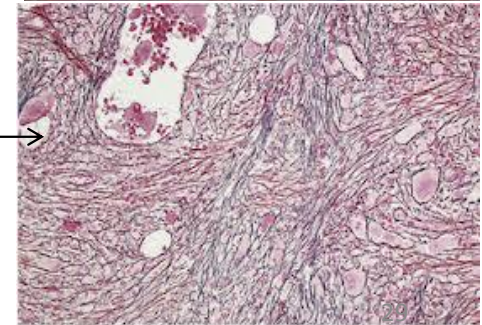
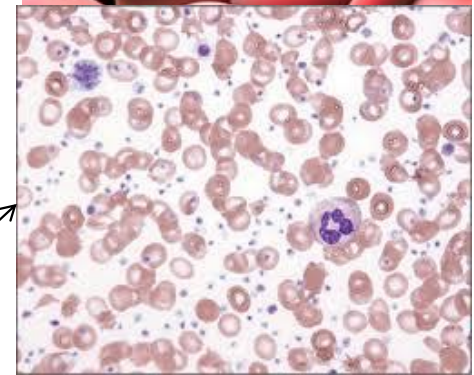
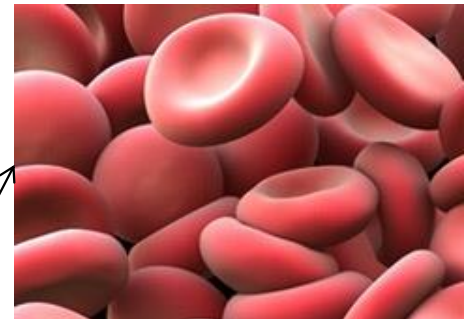
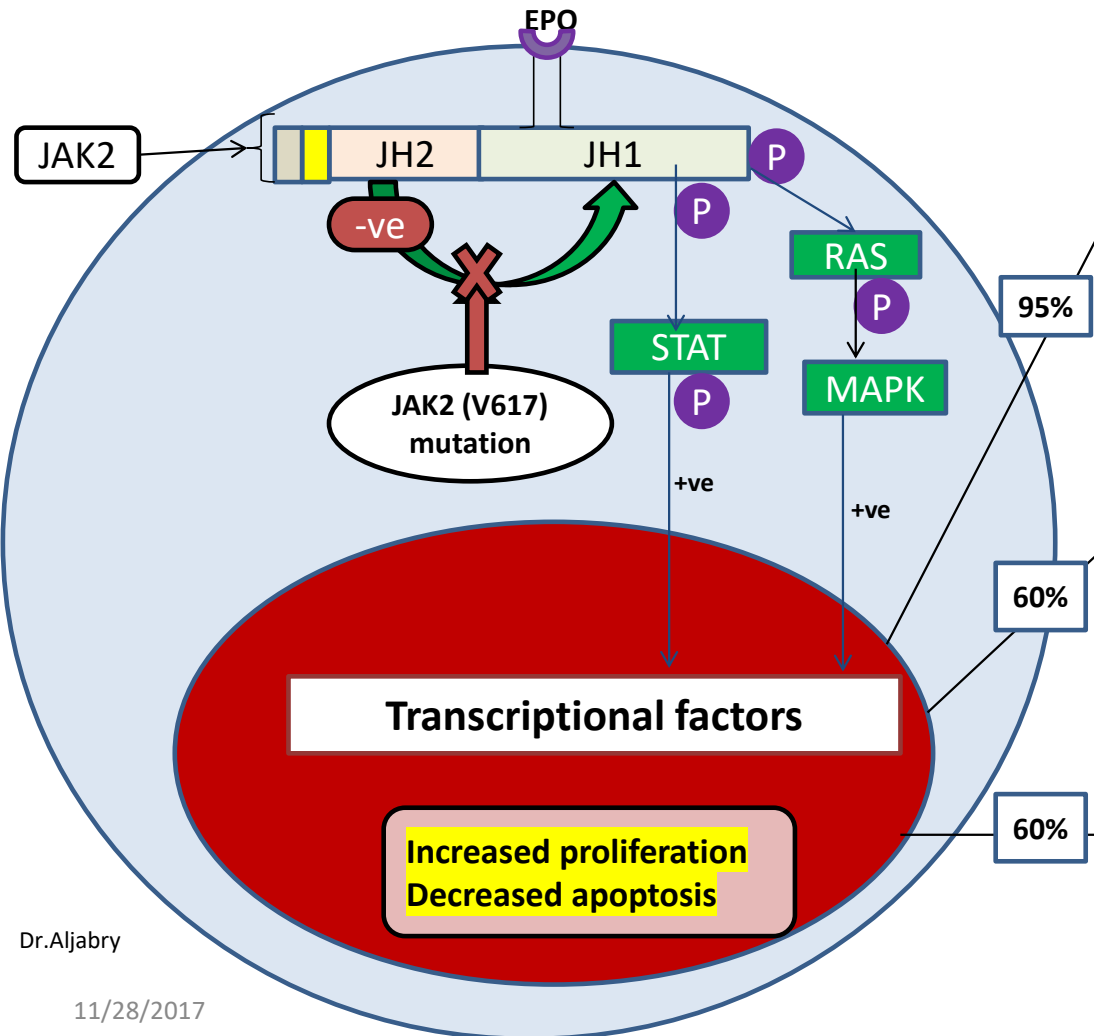
- **Point mutation (at codon 617 in JH2) leads to loss of auto inhibitory control over JAK2.**
- **The mutated JAK2 is in a constitutively active state.**

For reading





# JAK2 Mutation



ORIGINAL ARTICLE

# Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

Alessandro M. Vannucchi, M.D., Jean Jacques Kiladjan, M.D., Ph.D.,  
Martin Griesshammer, M.D., Tamas Masszi, M.D., Ph.D., Simon Durrant, M.D.,  
Francesco Passamonti, M.D., Claire N. Harrison, D.M., Fabrizio Pane, M.D.,  
Pierre Zachee, M.D., Ph.D., Ruben Mesa, M.D., Shui He, Ph.D.,  
Mark M. Jones, M.D., William Garrett, M.B.A., Jingjin Li, Ph.D.,  
Ulrich Pirron, Ph.D., Dany Habr, M.D., and Srdan Verstovsek, M.D., Ph.D.

**inib therapy on**

Srdan Verstovsek, M.D., Ph.D., Ruben A. Mesa, M.D., Jason Gotlib, M.D.,  
Richard S. Levy, M.D., Vikas Gupta, M.D., John F. DiPersio, M.D., Ph.D.,  
John V. Catalano, M.D., Michael Deininger, M.D., Ph.D., Carole Miller, M.D.,  
Richard T. Silver, M.D., Moshe Talpaz, M.D., Elliott F. Winton, M.D.,  
Jimmie H. Harvey, Jr., M.D., Murat O. Arcasoy, M.D., Elizabeth Hexner, M.D.,  
Roger M. Lyons, M.D., Ronald Paquette, M.D., Azra Raza, M.D.,  
Kris Vaddi, Ph.D., Susan Erickson-Viitanen, Ph.D., Iphigenia L. Koumenis, M.S.,  
William Sun, Ph.D., Victor Sandor, M.D., and Hagop M. Kantarjian, M.D.



# Q1)

- Which ONE of the following is NOT a cause of polycythemia?
- A) Mutation of *JAK-2*.
- B) Renal disease.
- C) Congenital heart disease.
- D) Hemoglobin abnormality.
- E) Iron overload.



## Q2)

- Which ONE of these statements is TRUE about pseudo (stress) polycythemia?
- A) It is caused by a raised red cell mass.
- B) It is associated with a large spleen.
- C) It is treated with hydroxycarbamide (hydroxyurea).
- D) It is most common in young male adults.

## Q3)

- What is the approximate frequency of the Val617Phe mutation in *JAK2* in myeloproliferative neoplasms?
- A) 99% in polycythemia vera (PV) and 50% in essential thrombocythemia (ET) and primary myelofibrosis (PM).
- B) Approximately 50% in PV, ET and PM.
- C) 50% in PV and 25% in ET and PM.
- D) 90% in PV, rare in ET and PM.

*Thank You!!!*