POLYCYTHEMIA

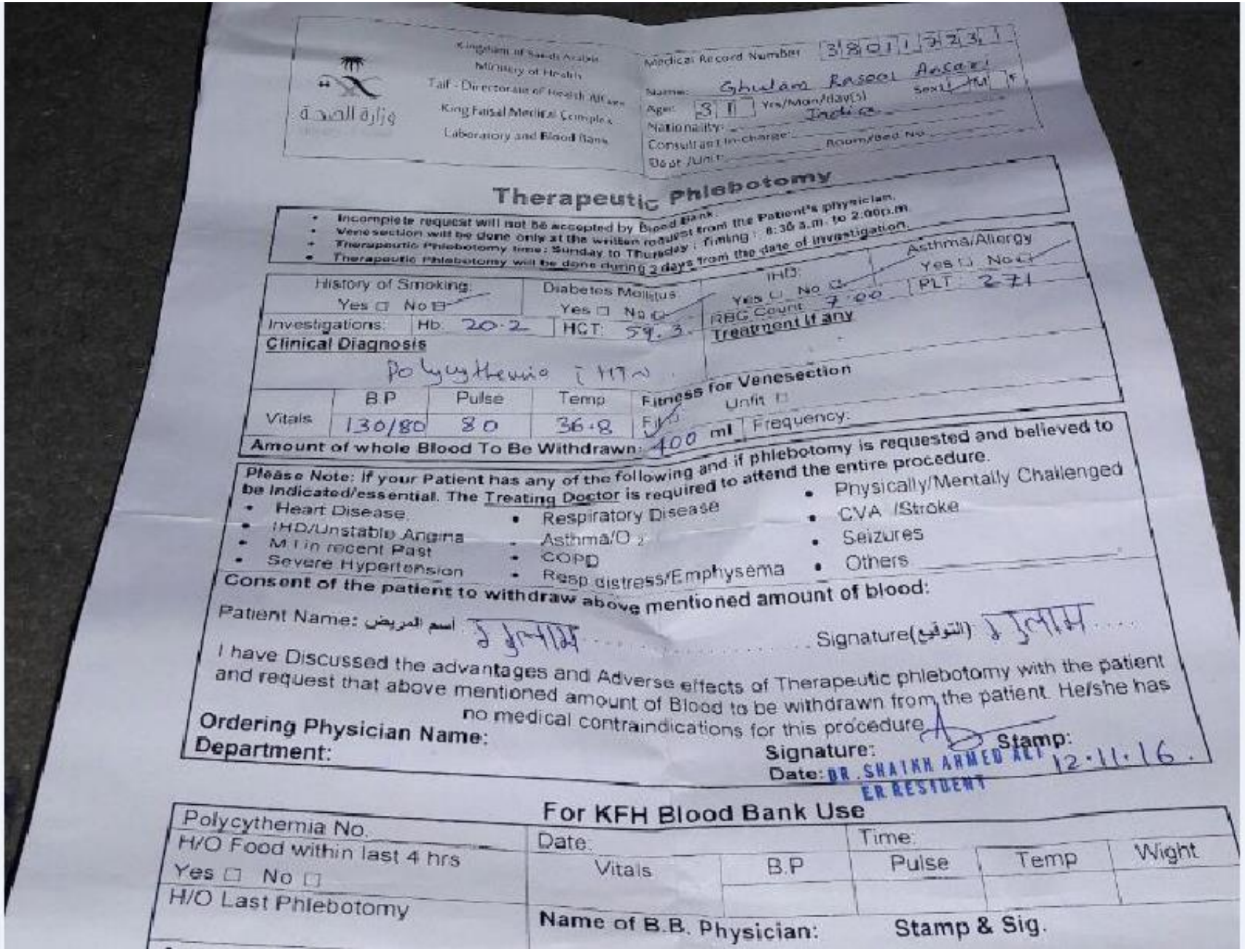
Dr. Alia Al-Faraedi

Consultant Haematologist

KKUH

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 about primary myelofibrosis and essential thrombocythemia.
- To appreciate the importance of genetic abnormalities (clonality) in these hematological neoplasms and the idea of targeted therapy.



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

وزارة الصحة

Medical Record Number: 3801/323/1

Name: Ghulam Rasool Ansari

Age: 31 Yrs/Mon/day(s) Sex: M / F

Nationality: India

Consultant In-charge:

Dept /Unit: Room/Bed No:

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 2.00p.m
- Therapeutic Phlebotomy will be done during 2 days from the date of investigation.

History of Smoking: Yes ☐ No ☒

Diabetes Mellitus: Yes ☐ No ☐

IHD: Yes ☐ No ☐

Asthma/Allergy: Yes ☐ No ☐

Investigations: Hb. 20.2 HCT: 59.3 RBC Count 7.00 PLT 271

Clinical Diagnosis

Polycythemia [HTN]

Treatment if any

	B.P	Pulse	Temp
Vitals	130/80	80	36.8

Fitness for Venesection

Fit ☐ Unfit ☐

Amount of whole Blood To Be Withdrawn: 400 ml Frequency: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 2
- 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 ..... Signature(التوقيع) .....

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and Adverse effects of Therapeutic phlebotomy with the patient and request that above mentioned amount of Blood to be withdrawn from the patient.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:

Stamp: DR. SHAIKH AHMED ALI ER RESIDENT

Date: 12.11.16.

For KFH Blood Bank Use

Polycythemia No.	Date:		Time:		
H/O Food within last 4 hrs Yes ☐ No ☐	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-ABL1*$^{+}$
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).**

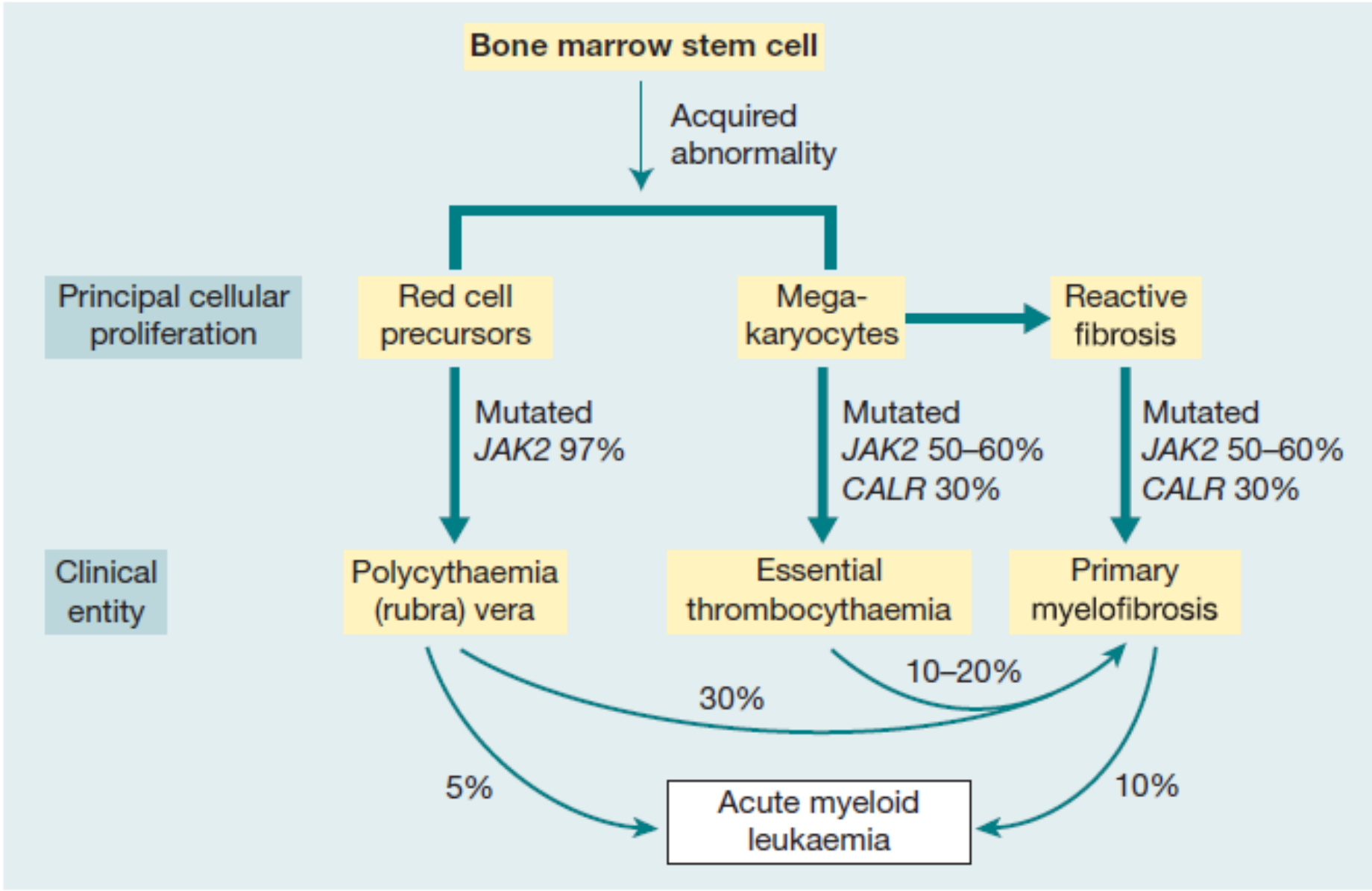
Table 1. Classification of Myeloid Neoplasms According to the 2008 World Health Organization Classification Scheme

1. **Myeloproliferative neoplasms (MPN)**
   - 1.1. Chronic myelogenous leukemia, *BCR-ABL1*–positive (CML)
   - 1.2. Polycythemia vera (PV)
   - 1.3. Essential thrombocythemia
   - 1.4. Primary myelofibrosis (PMF)
   - 1.5. Chronic neutrophilic leukemia
   - 1.6. Chronic eosinophilic leukemia
   - 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)**

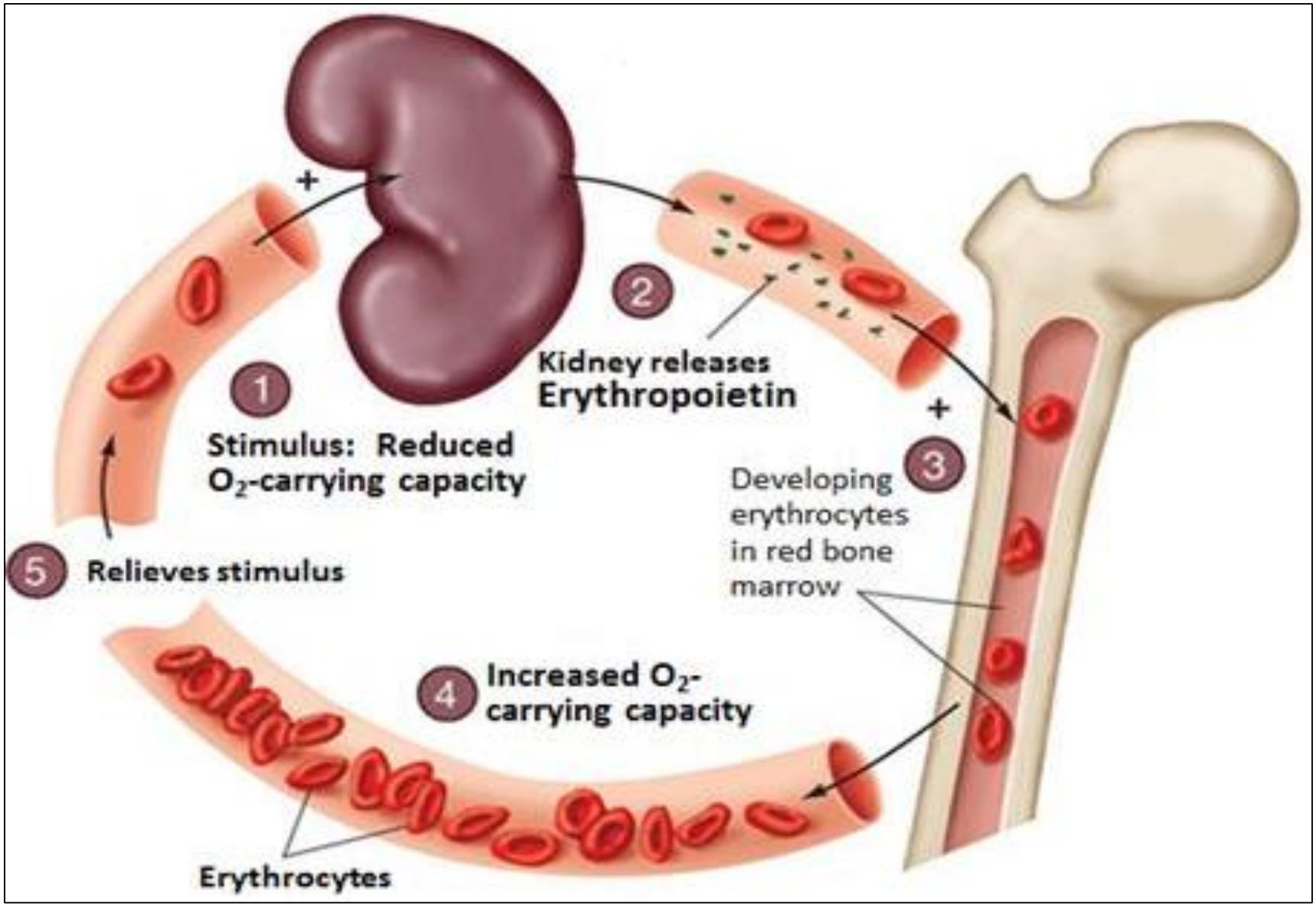
For reading


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%
10%
Acute myeloid leukaemia

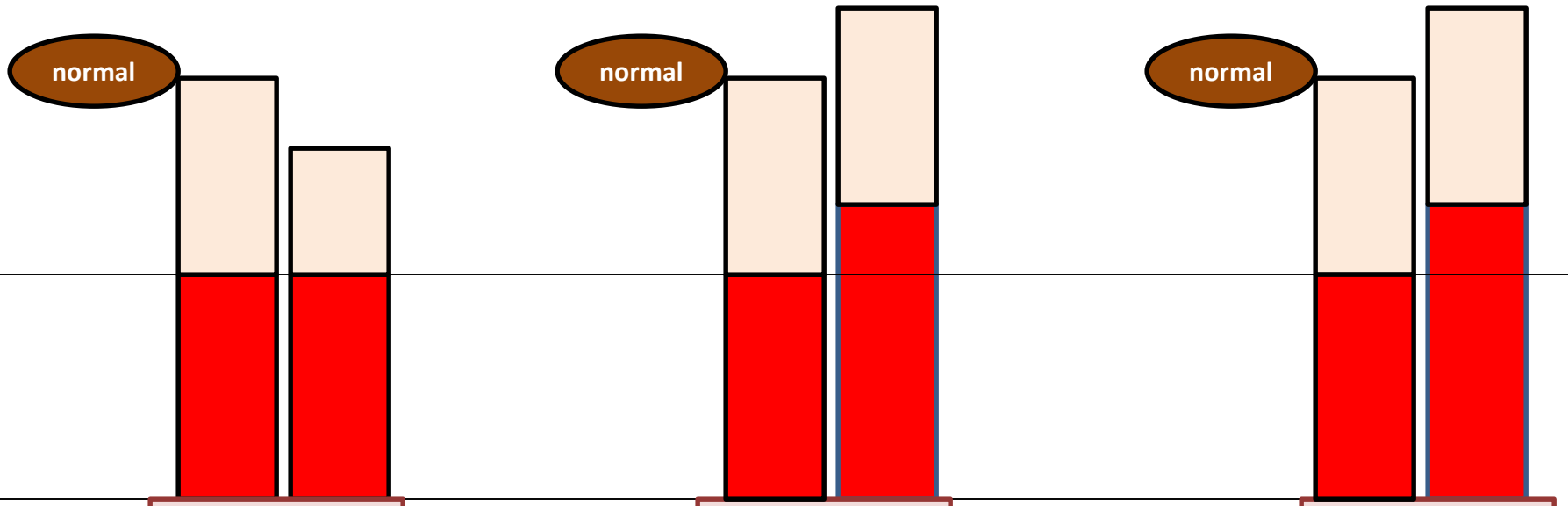
Polycythemia

- 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



Relative Polycythemia

Decreased plasma volume due to severe dehydration

2nd Polycythemia

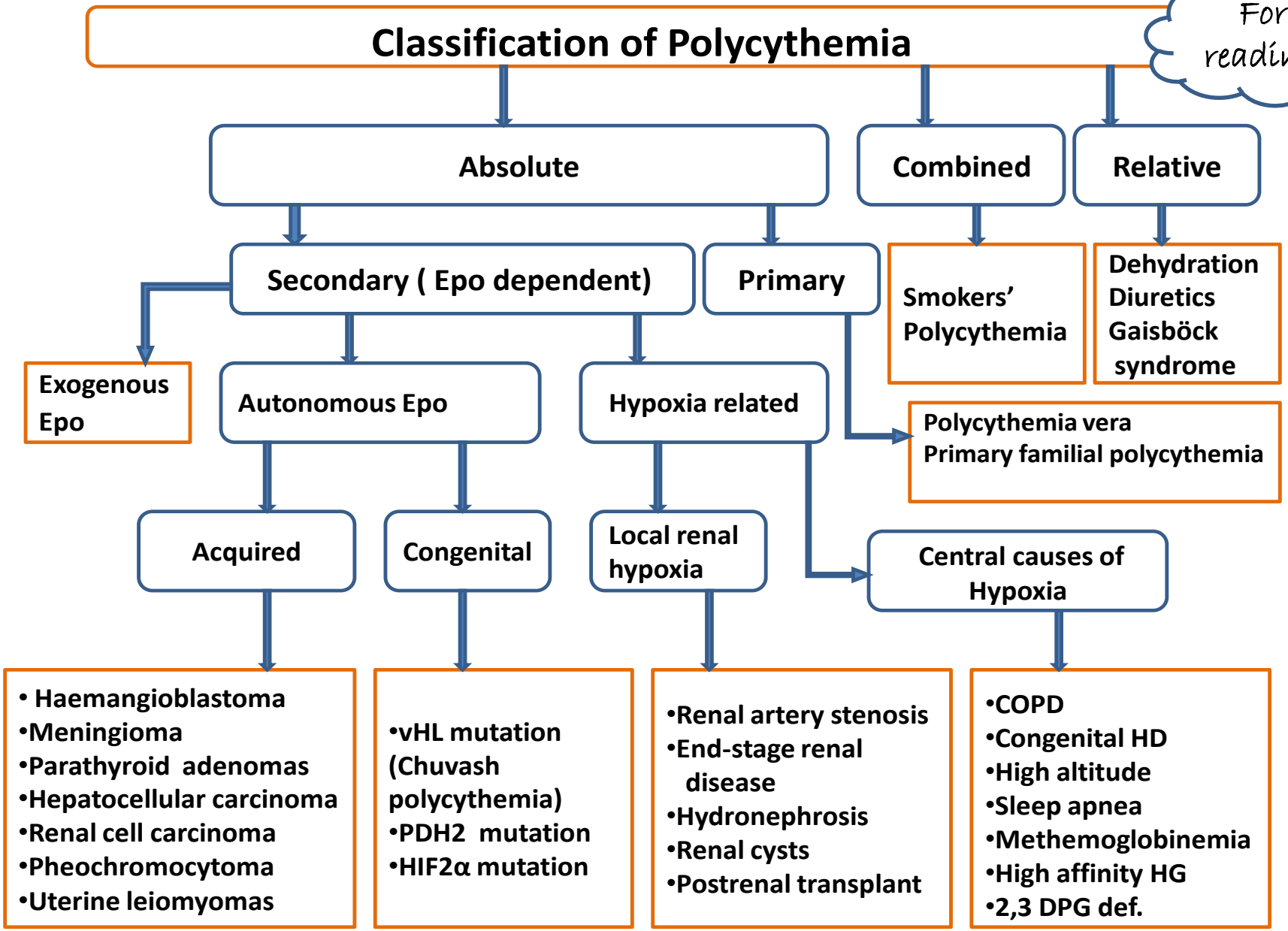
Increased RBC mass due to high EPO:
1-COPD, Sleep apnea, smoking..
2-High altitude
3-High affinity HB
4-Renal disease
5-Epo secreting tumor (Parathyroid adenoma …)

Polycythemia Vera

Increased RBC mass due to malignant proliferation

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

Updated WHO 2016

Table 4. WHO criteria for PV

WHO PV criteria
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 *JAK2*V617F 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

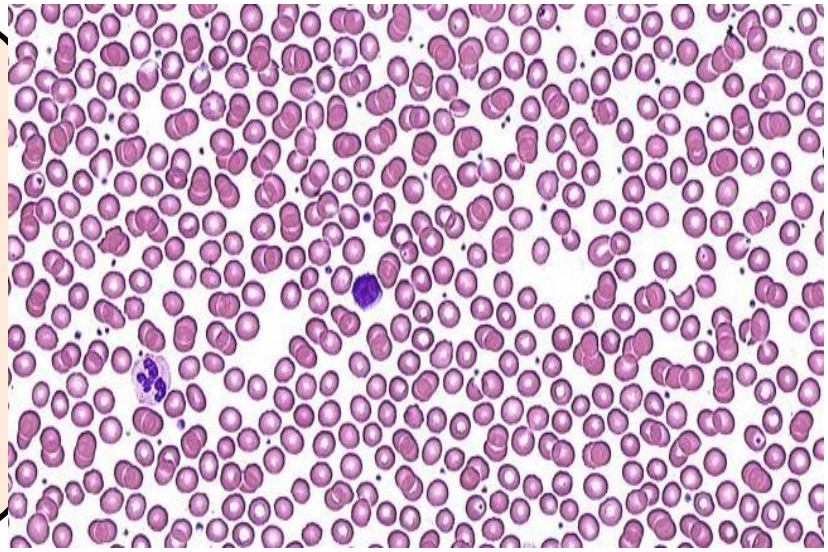
CBC:

*RBC: increased *Hb: increased

*WBC & PLT :mildly increased (usually).

Blood smear:

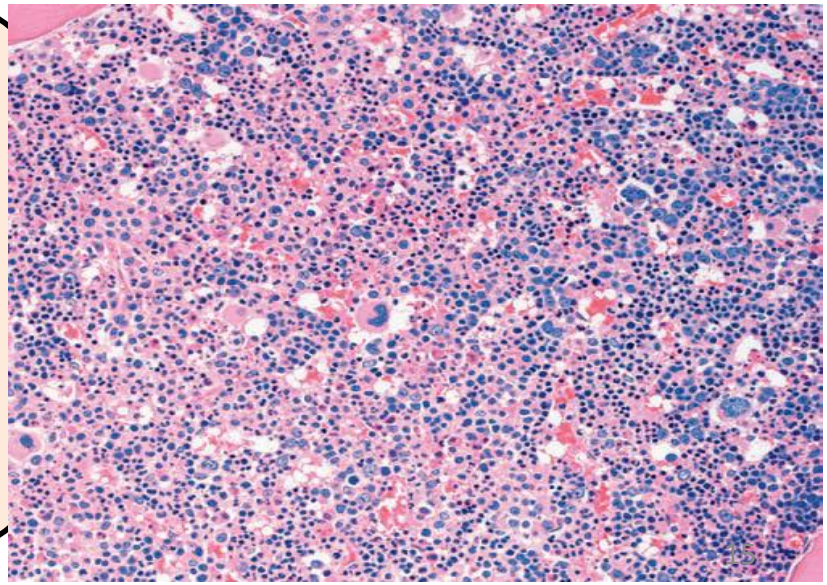
- Excess of normocytic normochromic RBC.
- ± Leukocytosis &thrombocytosis.



Bone marrow

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

↑ Blasts ⟶ AL transformation



Complication &treatment

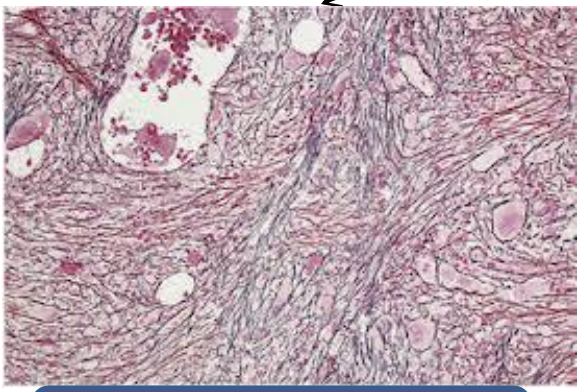
Diagnosis of Polycythemia Vera

Treatment:

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

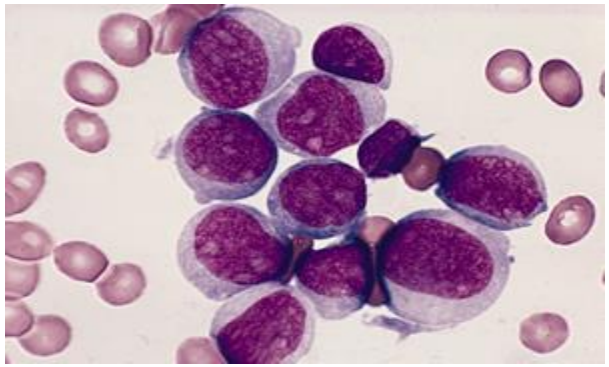
10-15 years

20-30%

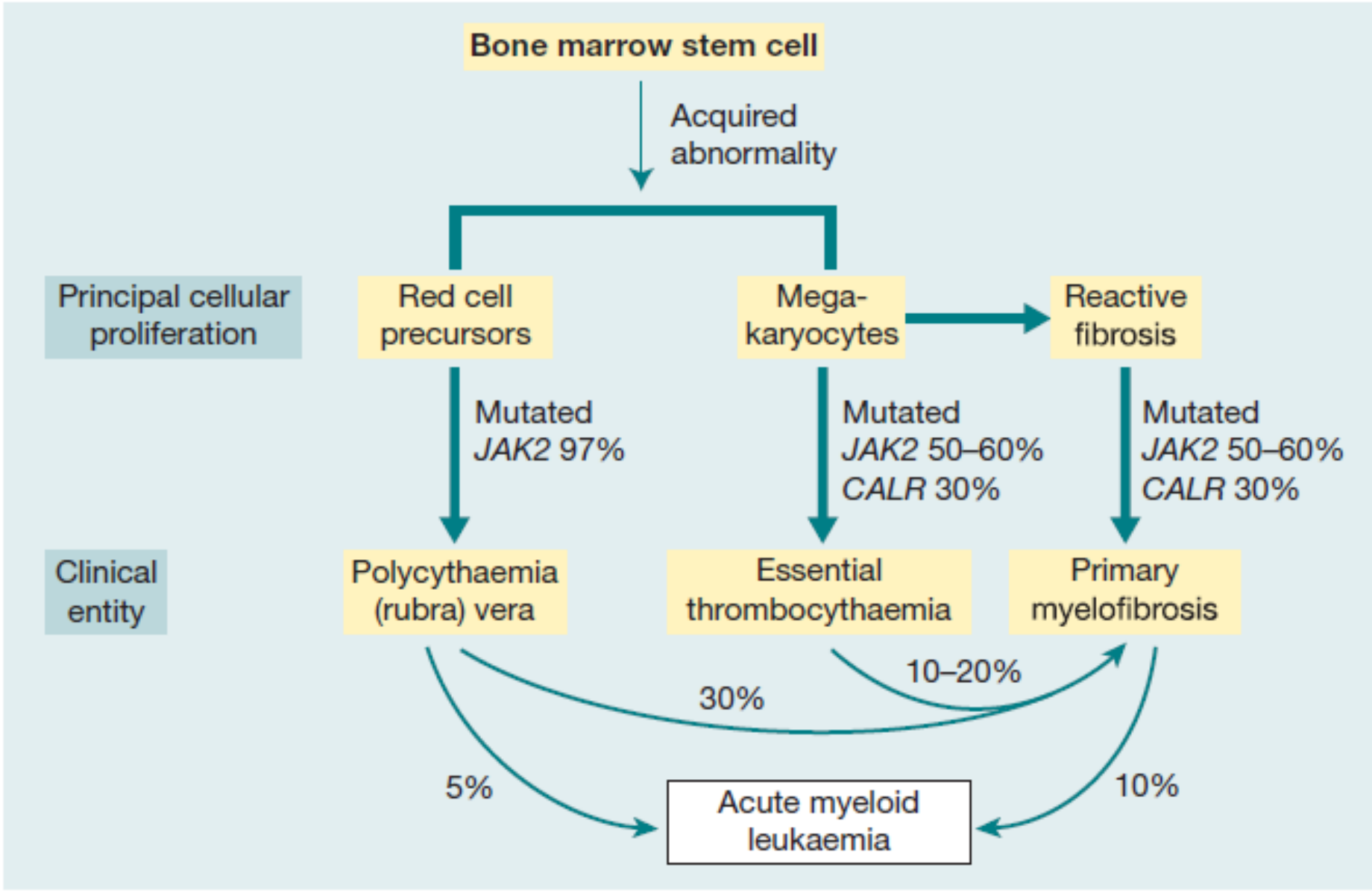


Myelofibrosis

5-10%



Acute leukemia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Essential thrombocythaemia
Primary myelofibrosis
30%
10–20%
5%
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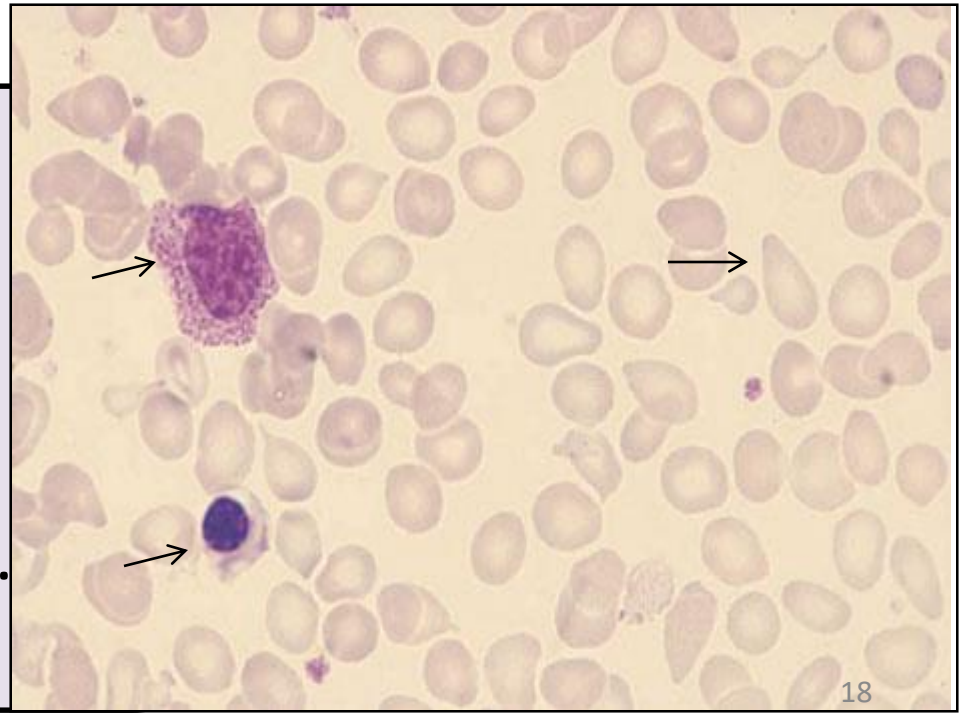
Acute myeloid leukaemia

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

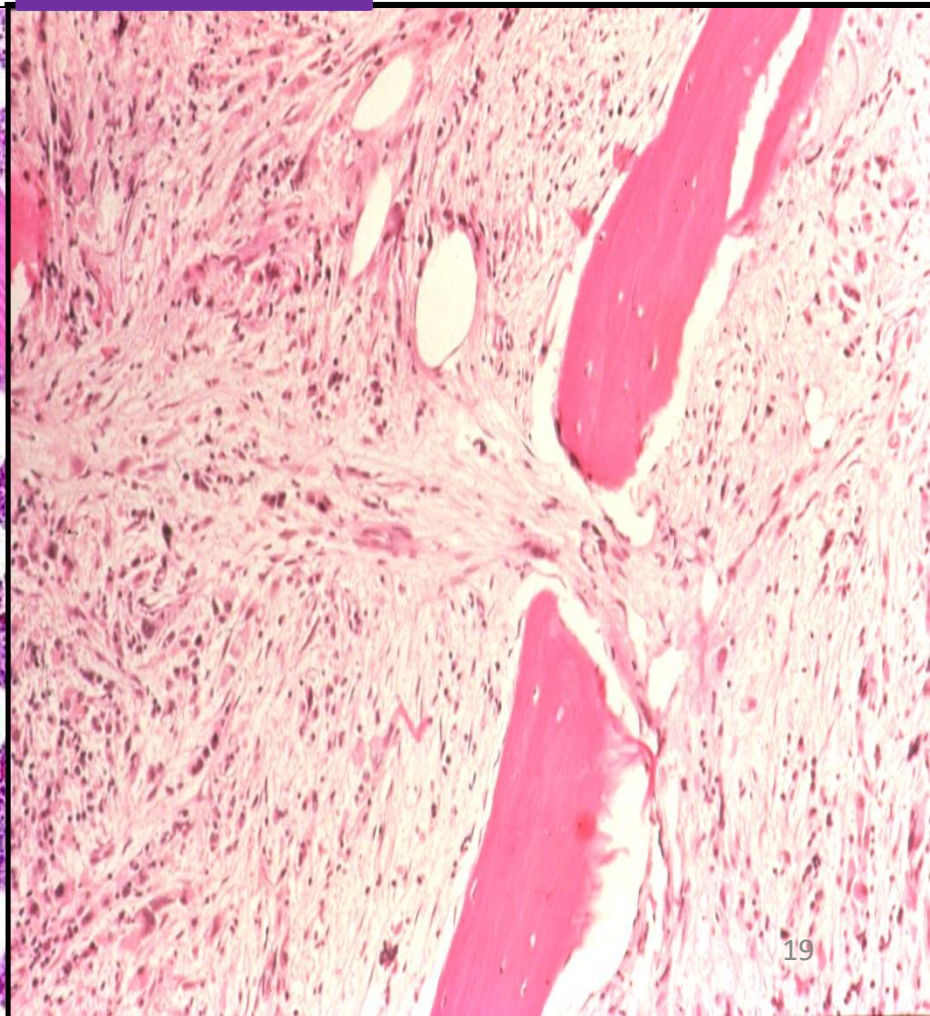
- Anemia
- Leukoerythroblastic blood picture.
- Massive splenomegaly.
- Fibrotic bone marrow.
- JAK2 mutation (50%-60%).
- Risk of AML transformation (10-20%).



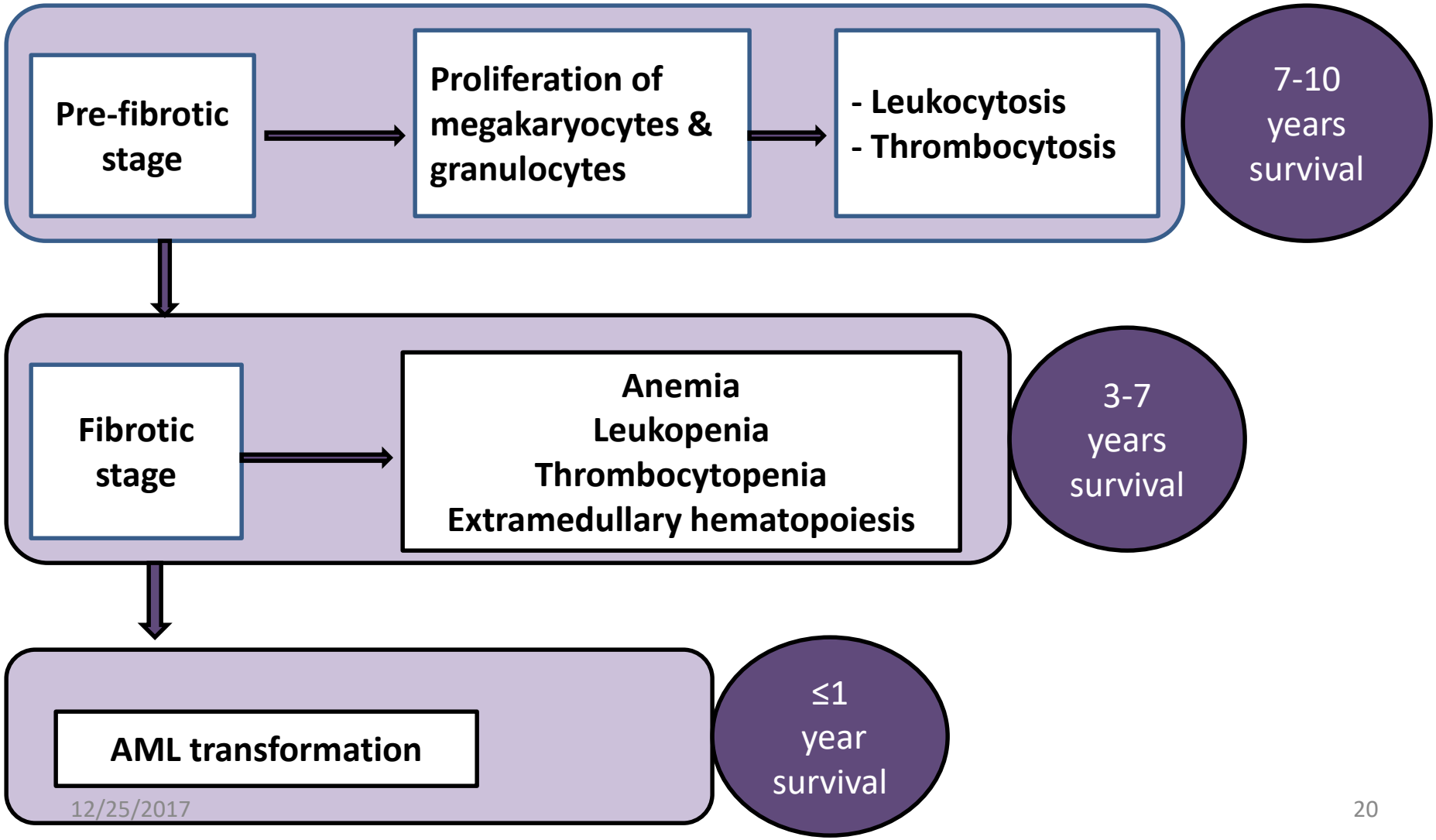
Bone marrow in Myelofibrosis

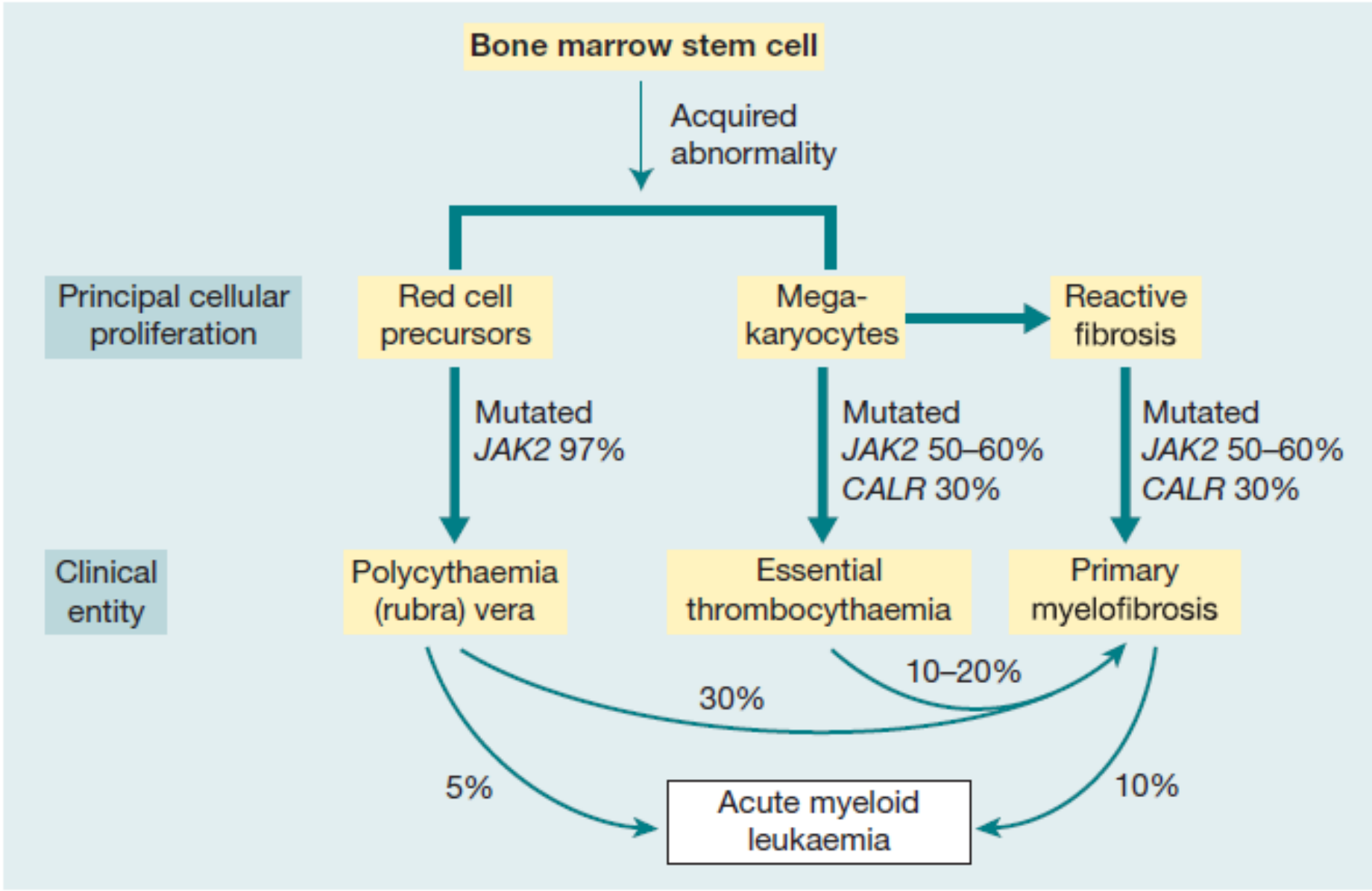
Normal BM

Fibrotic BM



Stages of PMF

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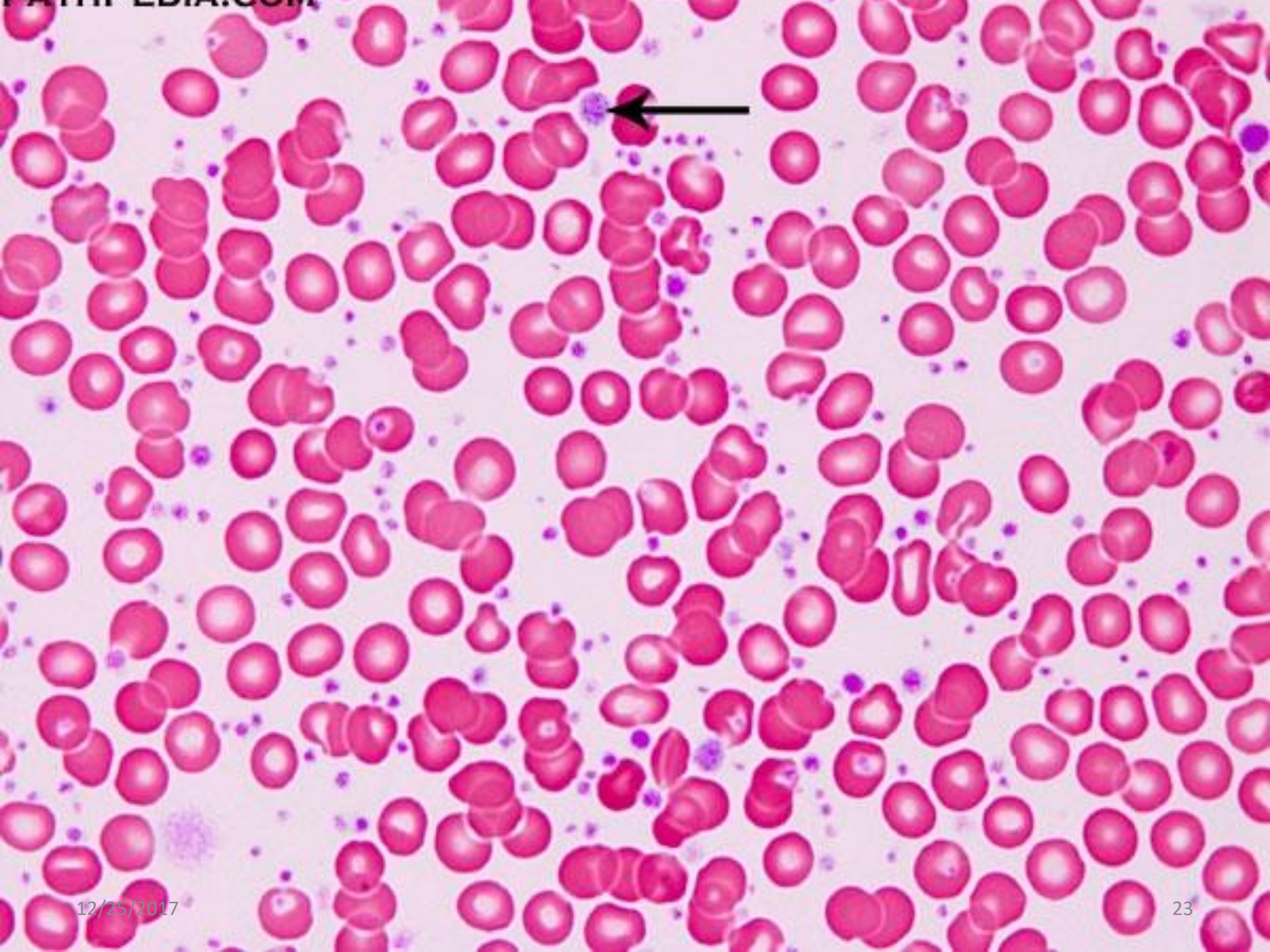
Essential Thrombocythemia

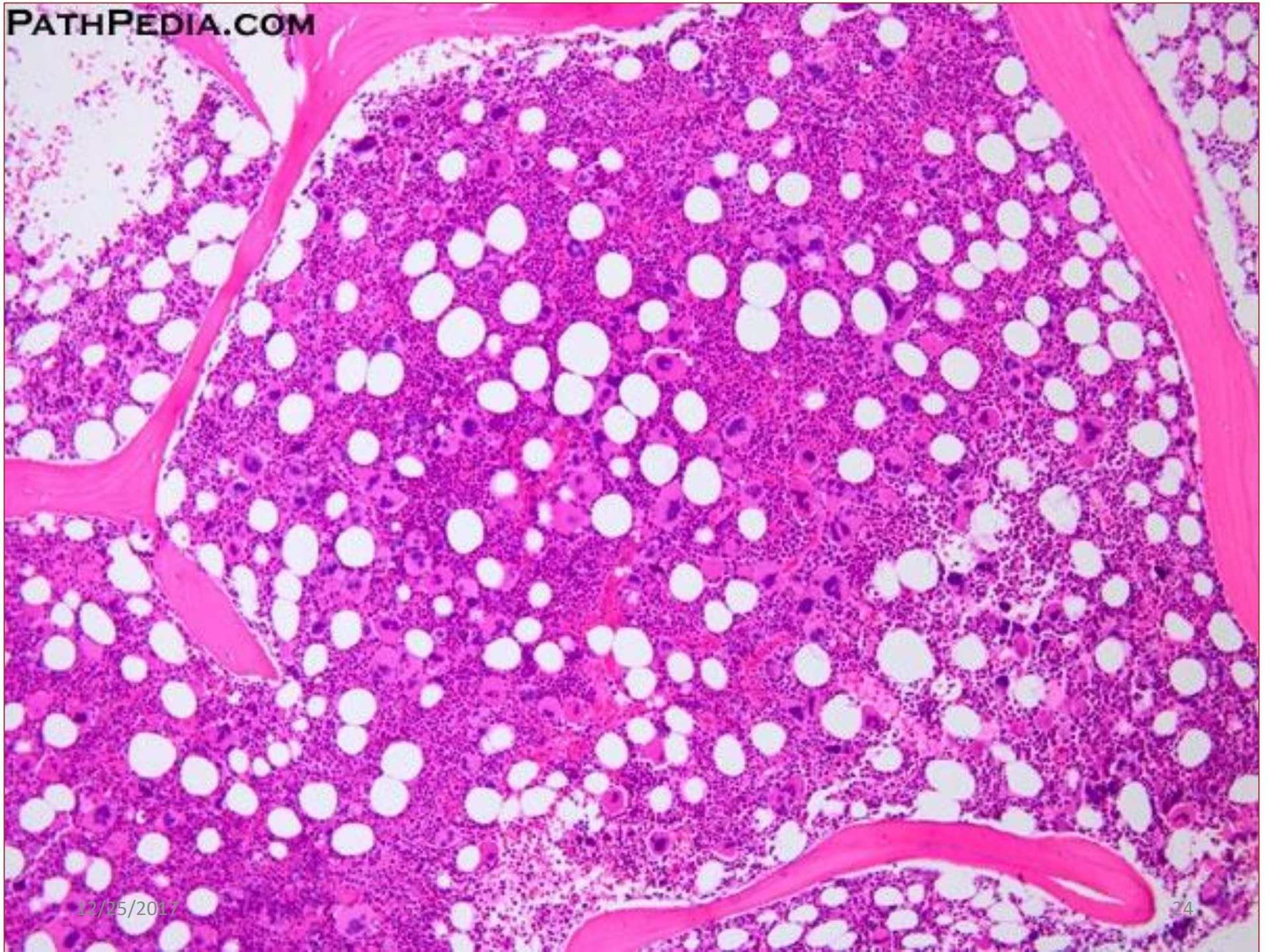
- It is a MPN that involves primarily the megakaryocytic lineage and characterized by sustained thrombocytosis .

Diagnostic Features

- Sustained thrombocytosis ≥45O×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….

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Essential Thrombocythemia

Clinical Presentation

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

Very indolent
(5% risk of AML transformation)

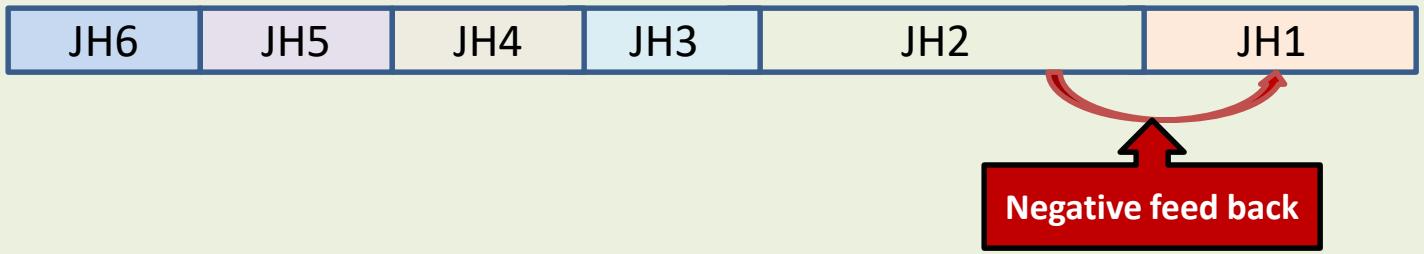
Treatment

Aspirin ± Hydroxyurea

JAK2 Mutation

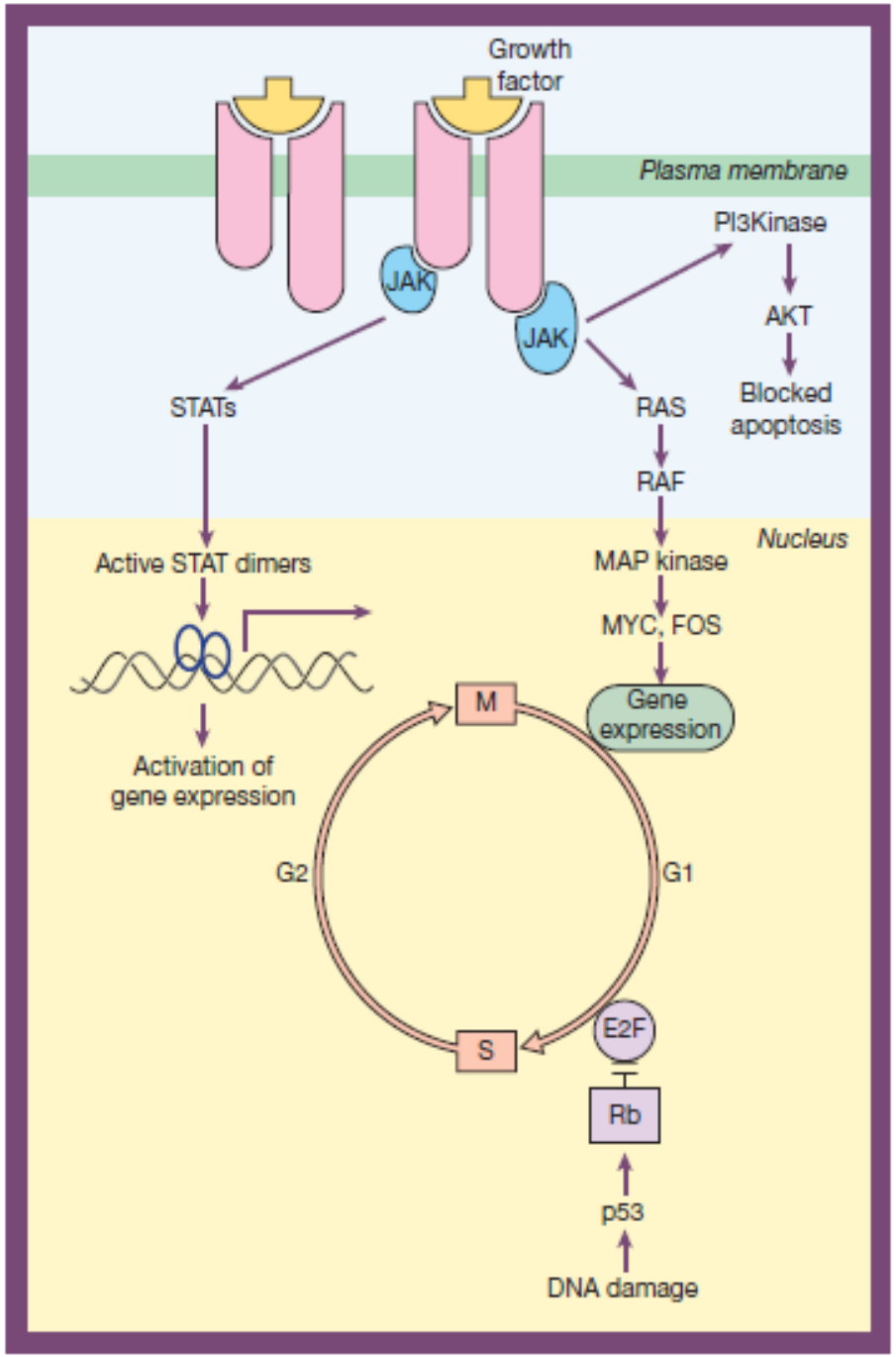
- **JAK2: (Ch 9p with 26 exons), a non-receptor protein tyrosine kinase involved in signal transduction pathway.**

JAK2 kinase domains structure



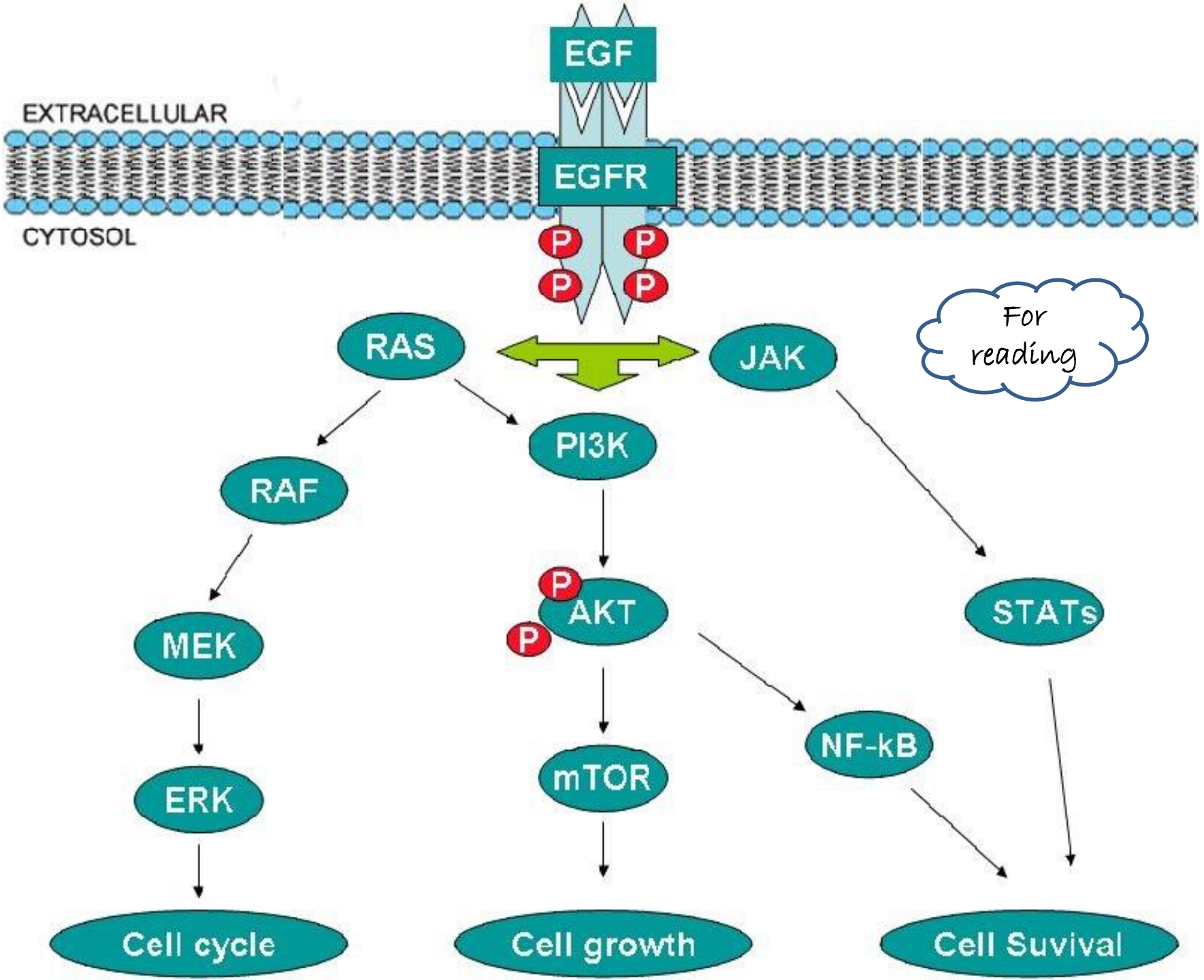
JAK2 mutation :

- **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

Hoffbrands Essential Haematology 7e 2016


EGF
EXTRACELLULAR
EGFR
CYTOSOL
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For reading
RAS
JAK
PI3K
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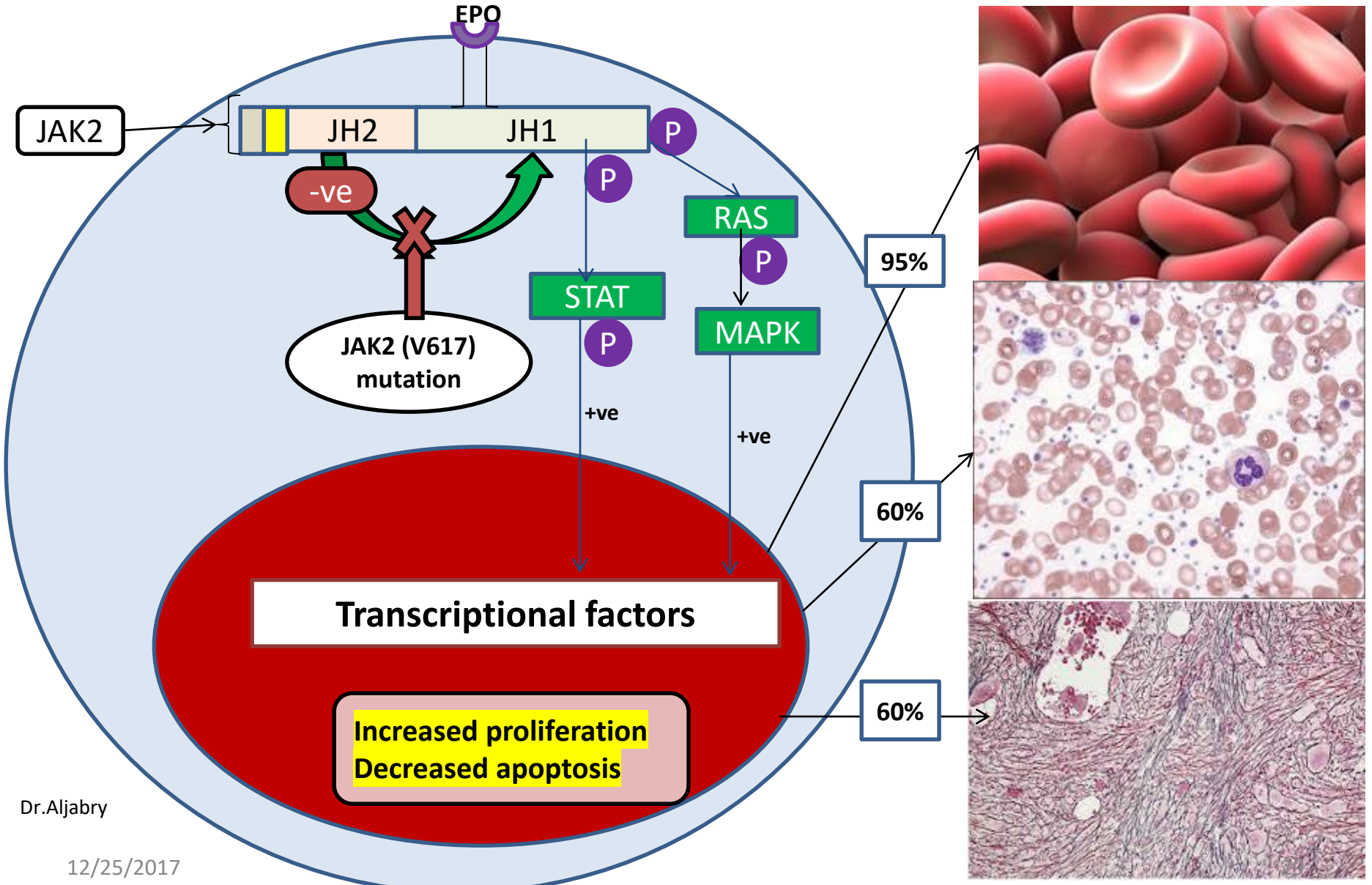
MEK
STATs
NF-kB
mTOR
ERK
Cell cycle
Cell growth
Cell Suvival

JAK2 Mutation



Dr.Aljabry

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

Alessandro M. Vannucchi, M.D., Jean Jacques Kiladjian, 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!!!