Myeloproliferative Neoplasms

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, not otherwise specified (CEL-NOS)
1.7. Mast cell disease (MCD)
1.8. MPN, unclassifiable

MPN features

- Cytosis
- Organomegaly (mainly splenomgaly)
- High uric acid
- Hypercellular bone marrow
- Progression to acute leukaemia (mainly AML)

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

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BCR-ABL must be negative

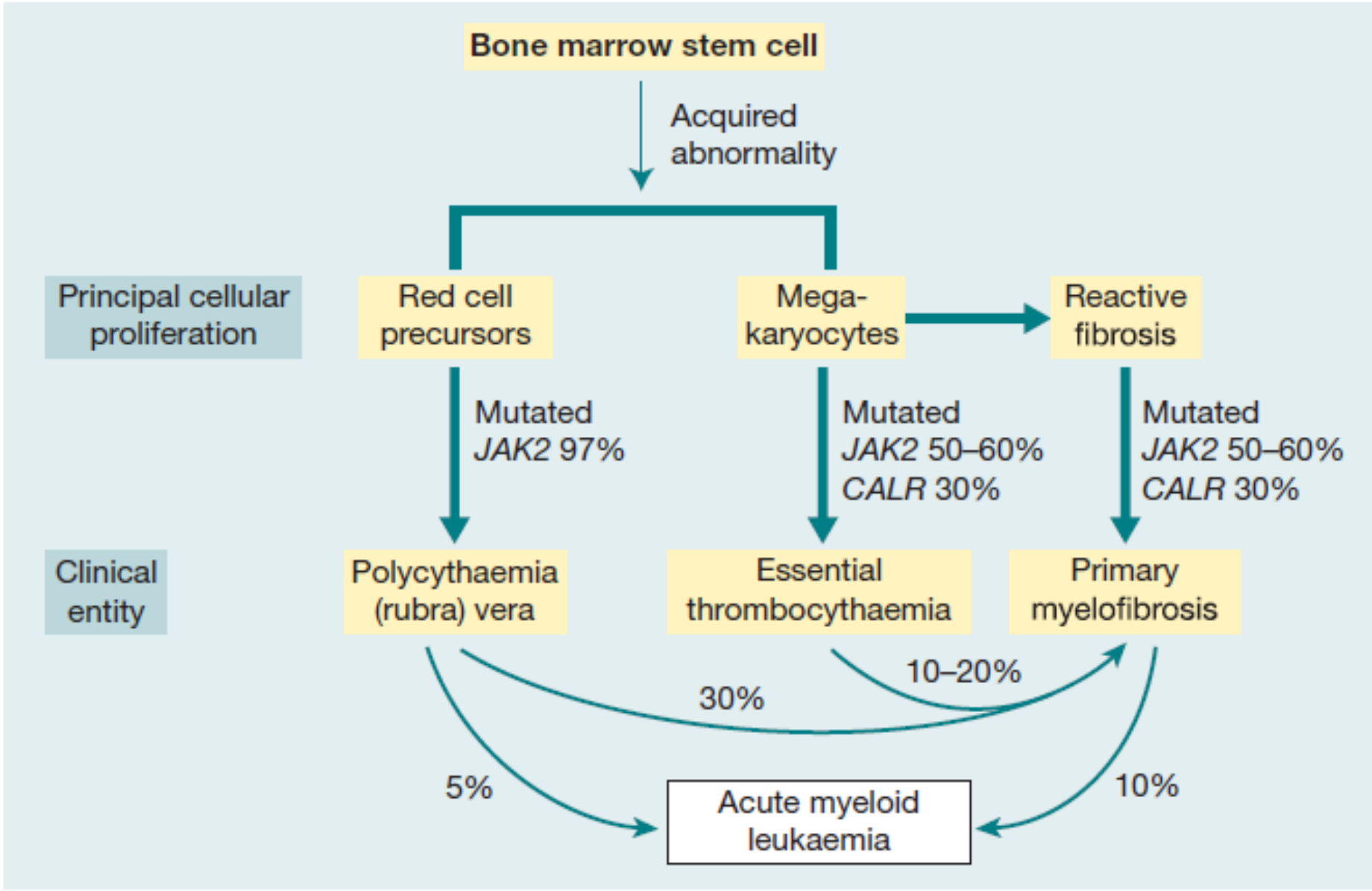
2. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1*

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)

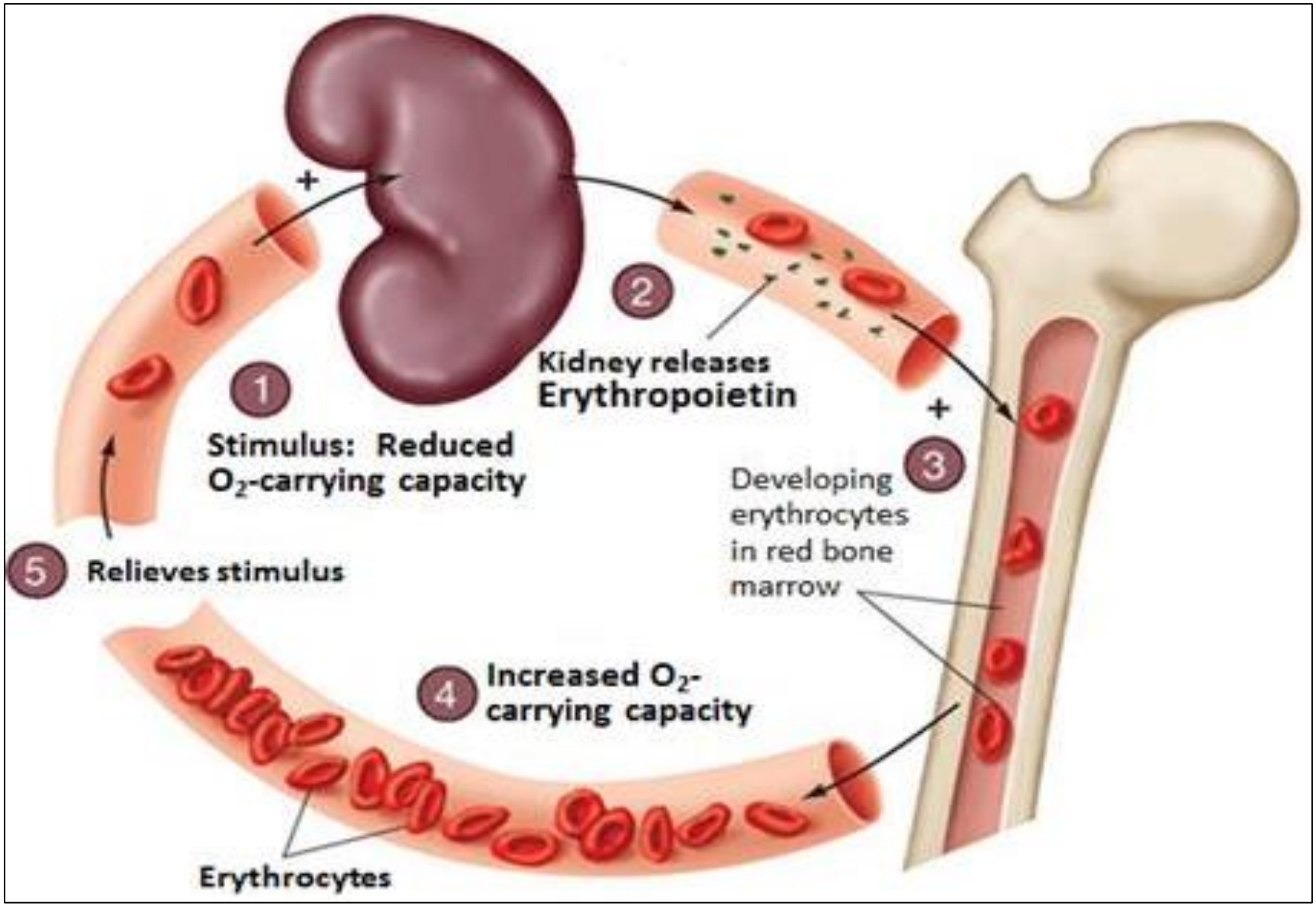
For reading


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
10–20%
30%
5%
10%
Acute myeloid leukaemia

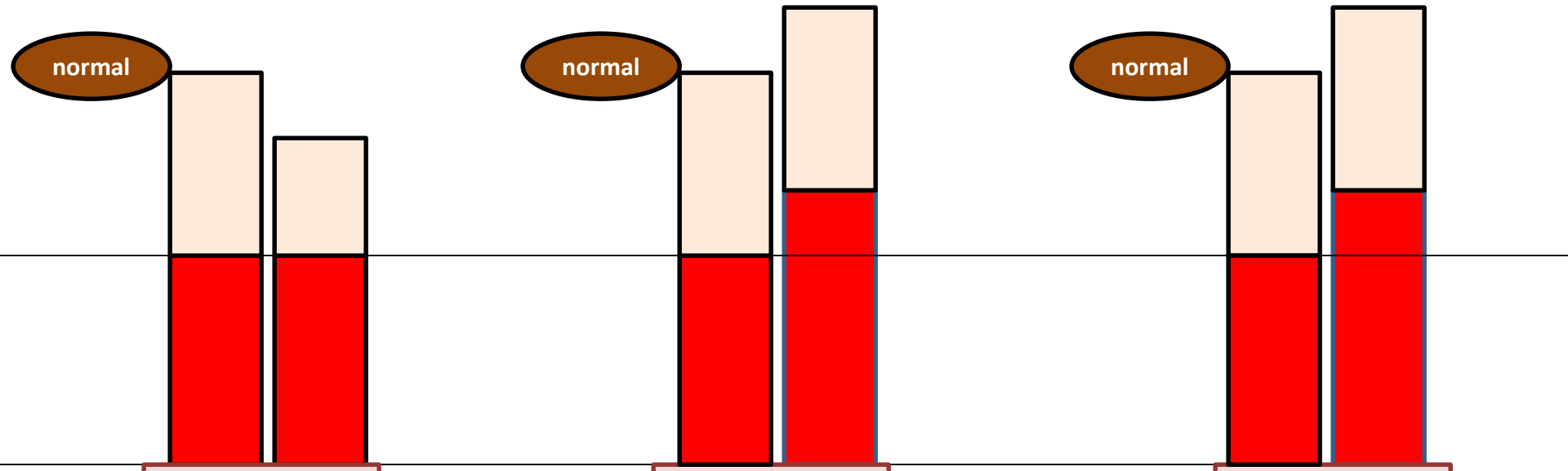
Polycythemia

- In Greek “too many cells in the blood.”.
- Absolute increase in total body red cell volume (or mass)
- Manifests itself as a raised Hb or packed cell volume (PCV)
- Hb is >16.5or 18.5 g/dl in women and men, respectively.

Regulation of Erythropoiesis



Classification of Polycythemia



Relative Polycythemia

Decreased plasma volume due to severe dehydration

2nd Polycythemia

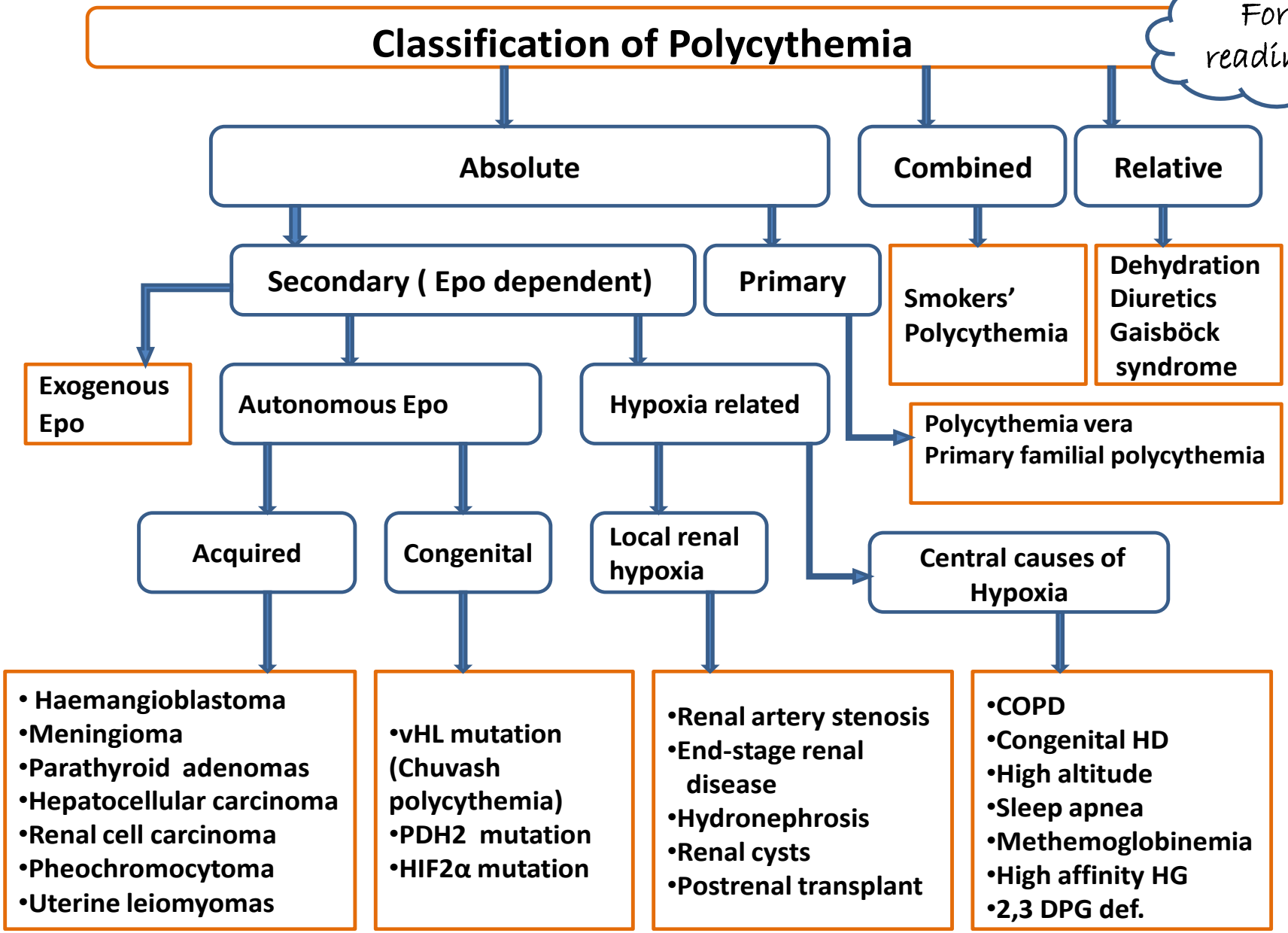
Increased RBC mass due to high EPO:
1-COPD, Sleep apnea, smoking..
2-High altitude
3-High affinity HB
4-Renal disease
5-Epo secreting tumor (Parathyroid adenoma …)

Polycythemia vera

Increased RBC mass due to malignant proliferation

Classification of Polycythemia

For reading



Polycythemia Vera

- **MPN characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis.**

Diagnostic Features:

- **HB >18.5g/dl in men ,16.5g/dl in women**
- **Hypercellular bone marrow**
- **JAK2 mutation in >95% of cases**
- **Low Serum erythropoietin level**

Polycythemia Vera

For reading

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**
- **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

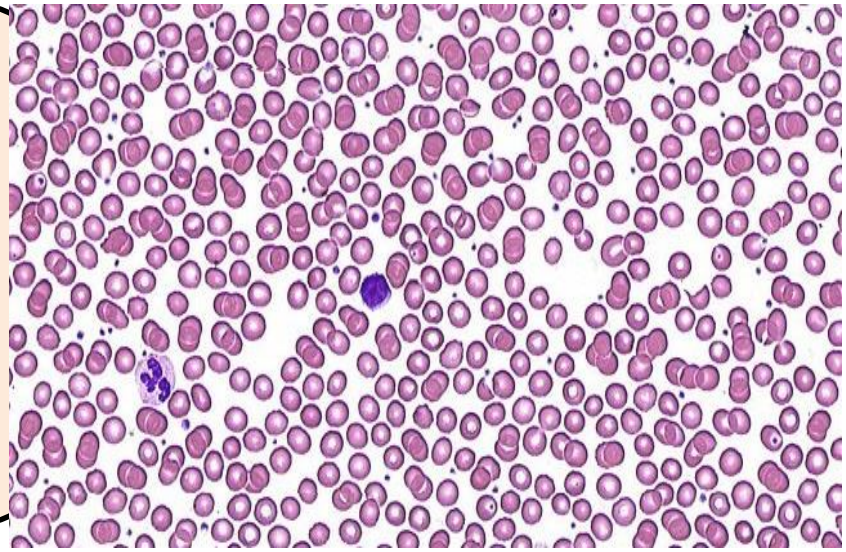
CBC:

*RBC: increased *Hb: increased

*WBC & PLT :mildly increased (usually)

Blood smear:

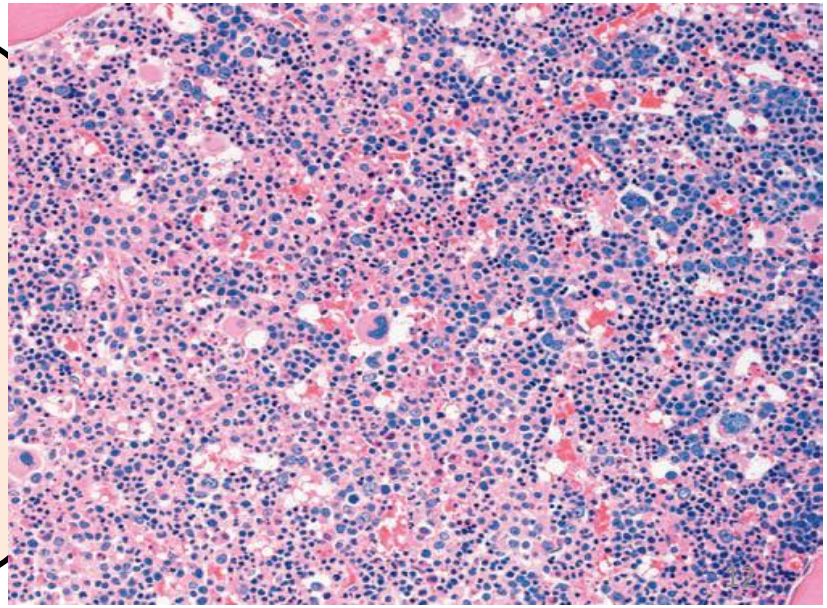
- Excess of normocytic normochromic RBC
- ±Leukocytosis &thrombocytosis



Bone marrow

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

↑ Blasts ⟶ AL transformation



Complication &treatment

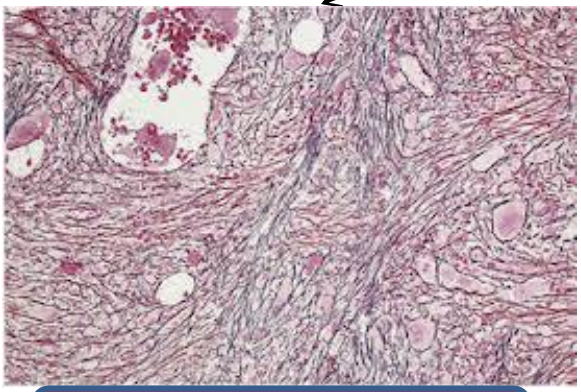
Diagnosis of Polycythemia Vera

Treatment:

- Venesection + Aspirin
- ± Myelosuppressive drugs (hydroxyuria)

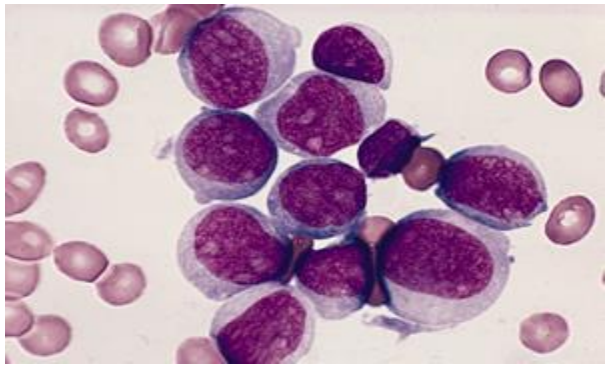
10-15 years

20%



Myelofibrosis

10%



Acute leukemia

Primary Myelofibrosis

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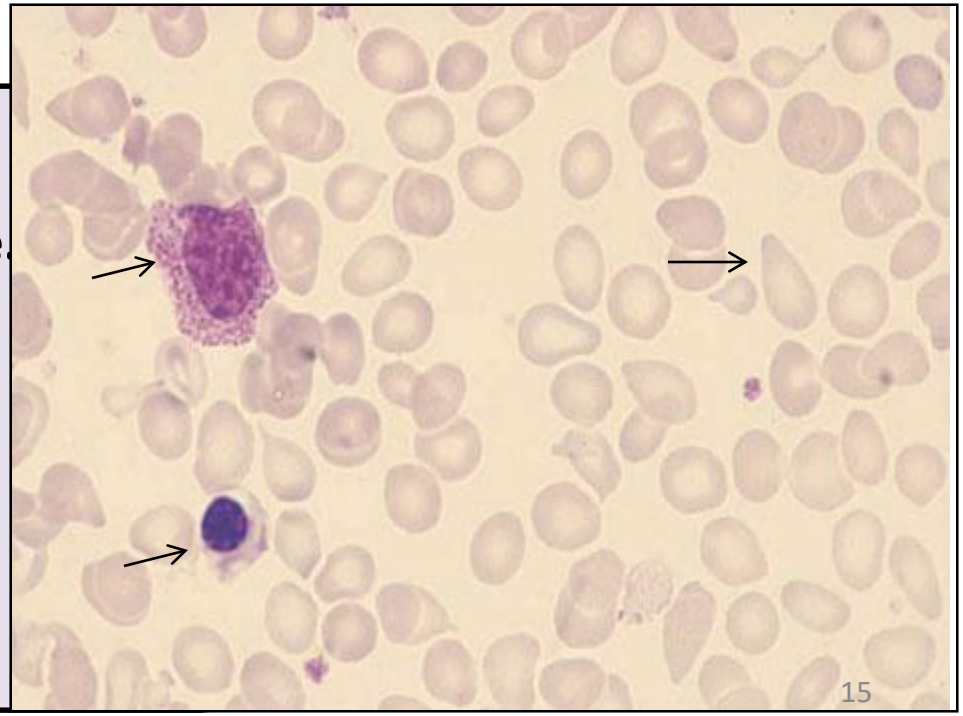
Primary Myelofibrosis

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

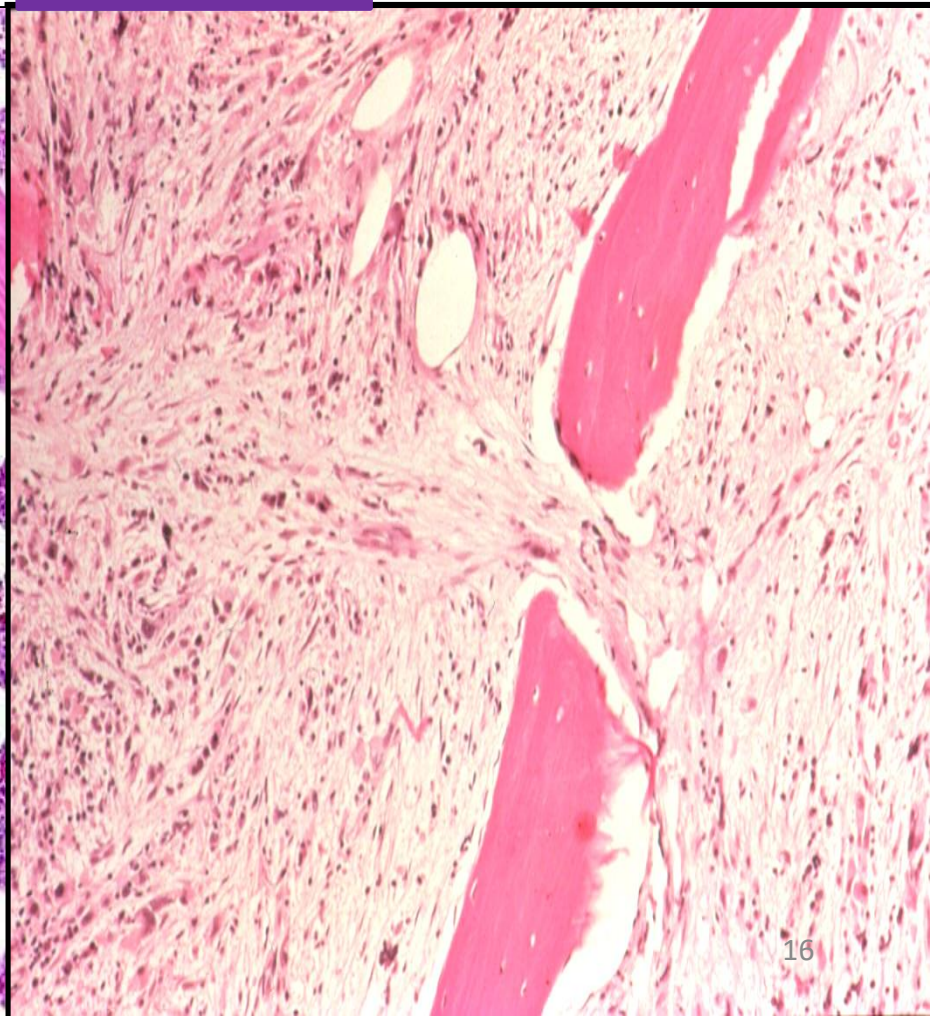
- Anemia
- Leukoerythroblastic blood picture.
- Massive splenomegaly
- Fibrotic bone marrow
- JAK2 mutation (50%)
- Risk of AML transformation (20%)



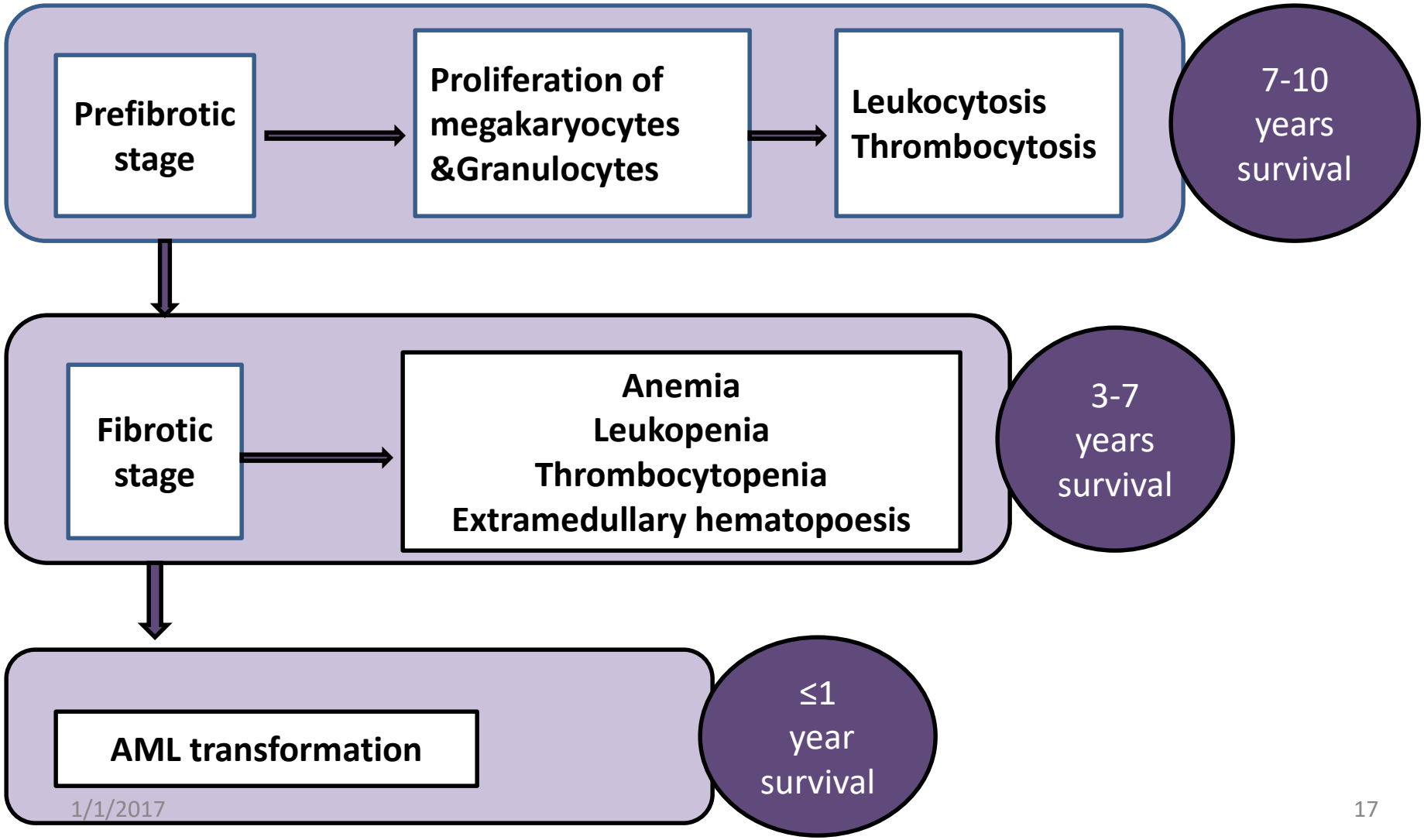
Bone marrow in Myelofibrosis

Normal BM

Fibrotic BM



Stages of PMF



Essential Thrombocythemia

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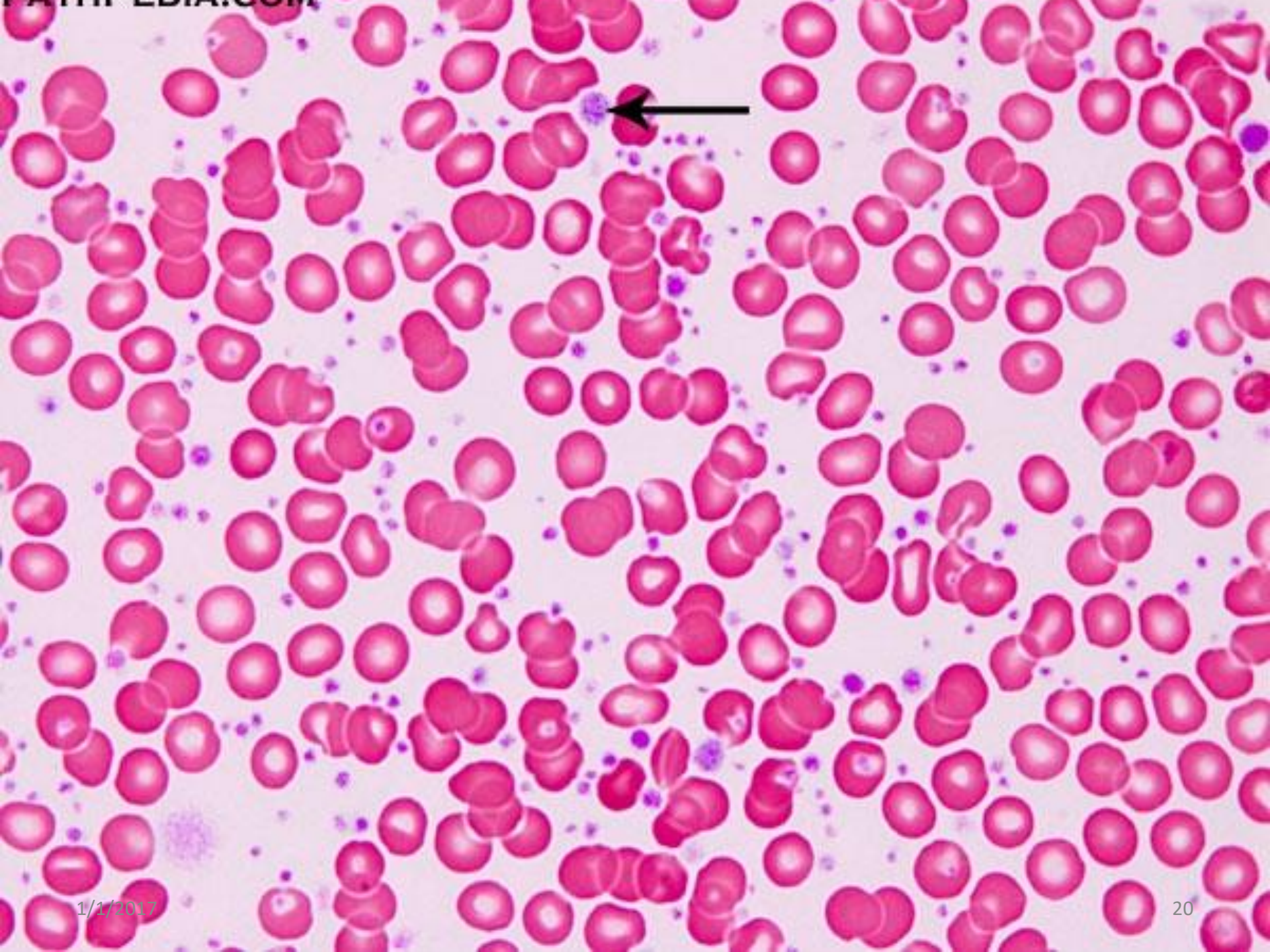
Essential Thrombocythemia

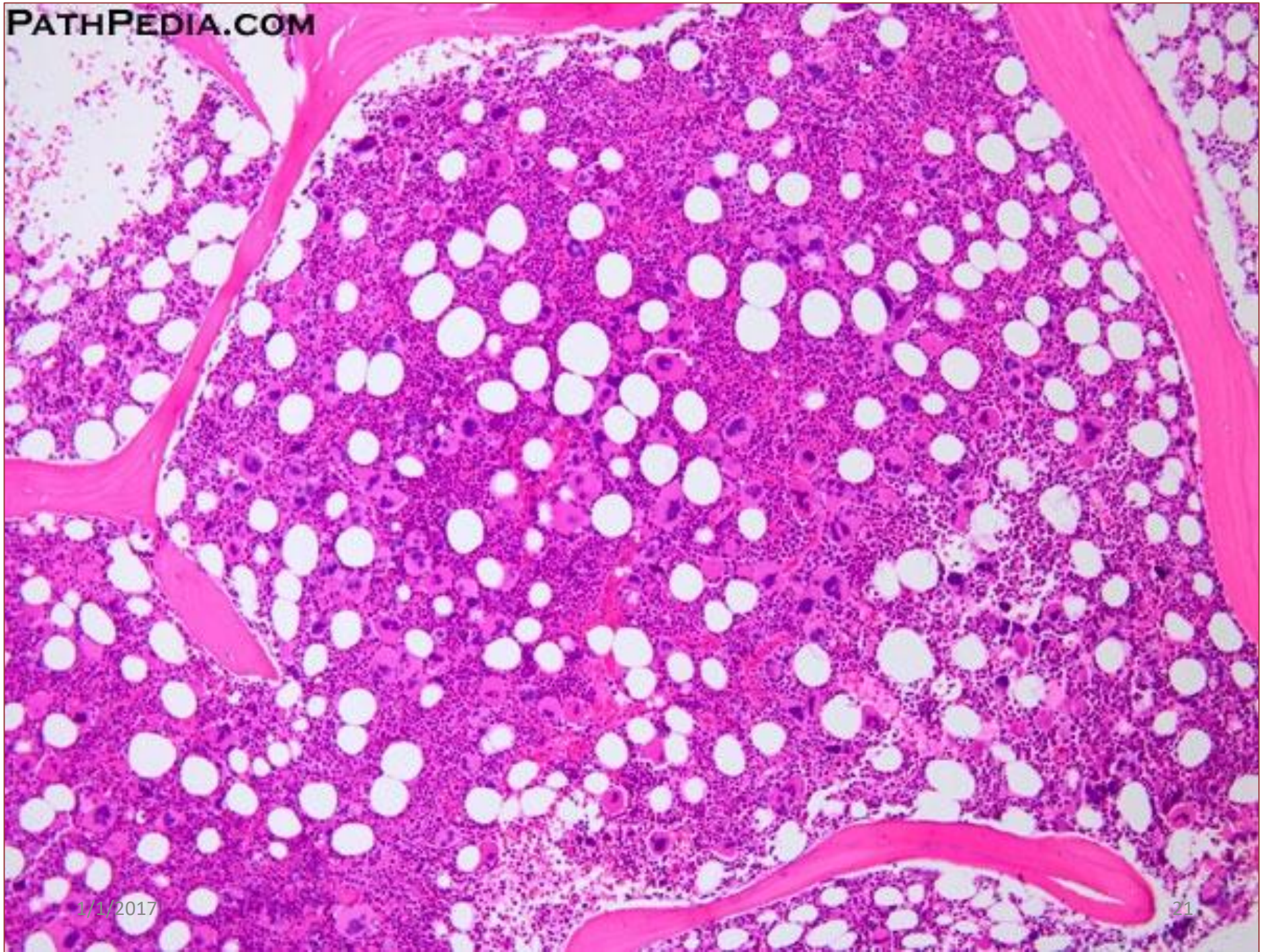
ET is MPN that involves primarily the megakaryocytic lineage. & characterized by sustained thrombocytosis .

Diagnostic Features

- **Sustained thrombocytosis ≥45O×10^9.**
- **Hypercellular BM with megakaryocytic proliferation**
- **Exclusion of: CML, MDS,PV &Primary Myelofibrosis**
- **JAK2 mutation (60%),If negative ;no evidence of reactive thrombocytosis:**

Iron def. ,splenoctomy, 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)

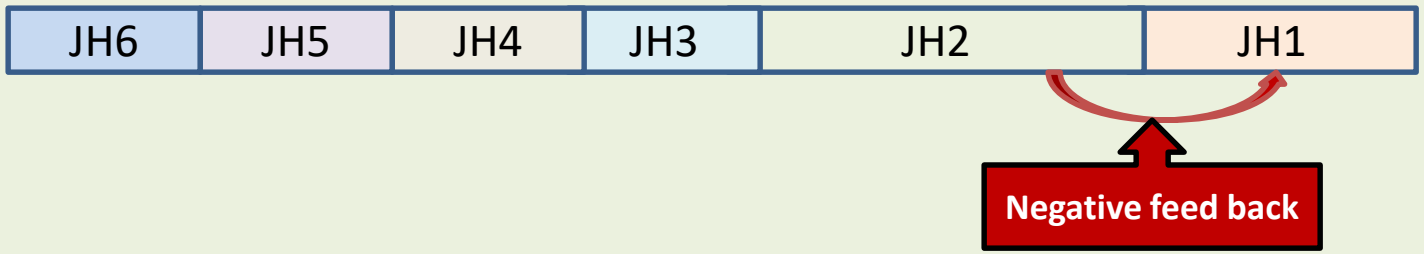
Treatment

Aspirin ±Hydroxyuria

JAK2 Mutation

JAK2: Non receptor protein tyrosine kinase involved in signal transduction pathway

JAK2 kinase domains structure

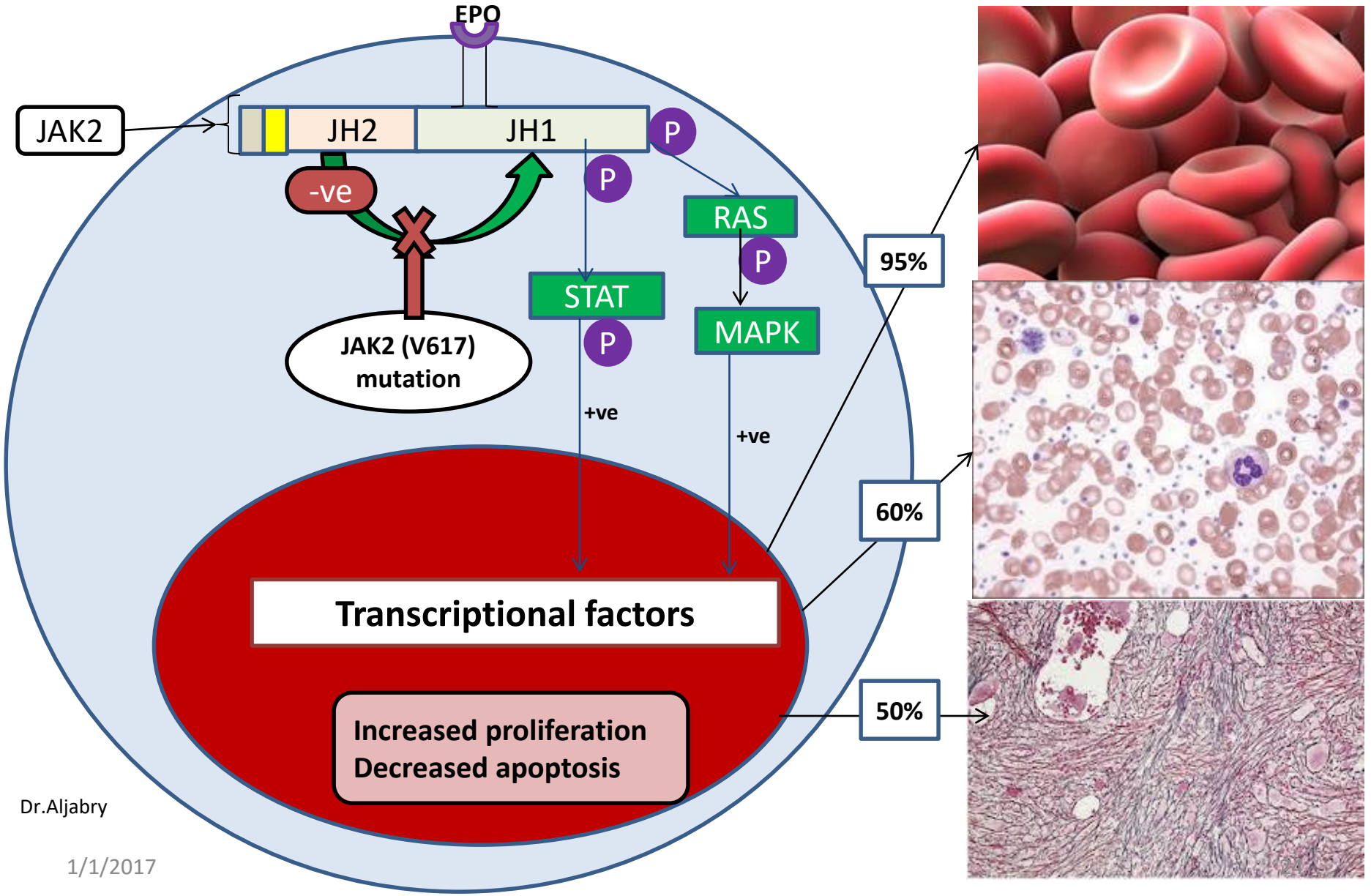


JAK2 mutation :

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,

JAK2 Mutation



Dr.Aljabry

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ORIGINAL ARTICLE

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

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