myelogenous leukaemia, that can be identified via its distinctive BCR-ABL translocation.

■ **To complete diagnosis of idiopathic myelofibrosis Criteria:** Thrombocytosis > 450.10^9/L, increased red-cell mass (> 25 % of the predicted value), presence of immature myeloid cells in peripheral blood, (leukoerythroblastosis with dacryocytes or teardrop cells, atypical platelets, and circulating giant megakaryocytes).

■ **To confirm a clonal hematopoietic stem cell disorder.**

■ **To confirm MPD in cases with high erythrocyte, leukocyte, or platelet counts.**

■ **To diagnose MPDs,** even latent, in cases of portal, mesenteric vein thromboses and Budd-Chiari Syndrome. JAK2 mutation should be investigated in patients with splanchnic vein thrombosis as half of the PV and ET cases show thrombotic complications.

Specimen Requirements

- **Collect:** 2 X 5 mL whole blood sample (EDTA, lavender top tube).
- **Testing Information:** TaqMan Allelic discrimination & quantitation Detection sensitivity ~2%.
- **Stability:** Maintain sample at room temperature (24 hours) or refrigerator temperature (4 days) - do not freeze.
- **Price:** Please contact the International Team for pricing details.

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Focus on...

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SPECIALISED MEDICAL PATHOLOGY

JAK2 V617F Mutation and myeloproliferative disorders (MPDs)

Septembre 2007

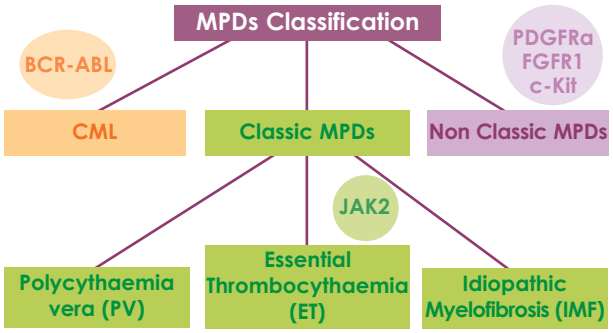
Myeloproliferative Disorders (MPDs)

MYELOPROLIFERATIVE DISORDERS (MPDs) are heterogeneous diseases that occur at the level of multipotent hematopoietic stem cells. They are characterised by increased blood cell production related to cytokine hypersensitivity and abnormal cell maturation. These disorders are haematological malignancies that arise from the transformation of a multipotent haematopoietic stem cell. These disorders can be divided into three groups:

■ **Chronic myeloid leukaemia (CML)** is a myeloproliferative disorder that is defined by its causative molecular lesion, the BCR-ABL fusion gene, which most commonly results from the Philadelphia translocation t(9;22).

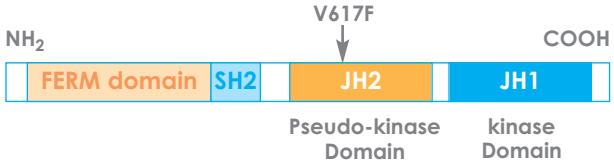
■ **Classic MPDs (Ph-negative myeloproliferative disorders)** comprising polycythaemia rubra vera which is also know as polycythaemia vera (PV), essential thrombocythaemia (ET) and idiopathic myelofibrosis (IMF).

■ **Non classic MPDs** including chronic neutrophilic leukaemia (CNL), hypereosinophilic syndrome /chronic eosinophilic leukaemia (HEL/CEL) and other unclassifiable myeloproliferations.

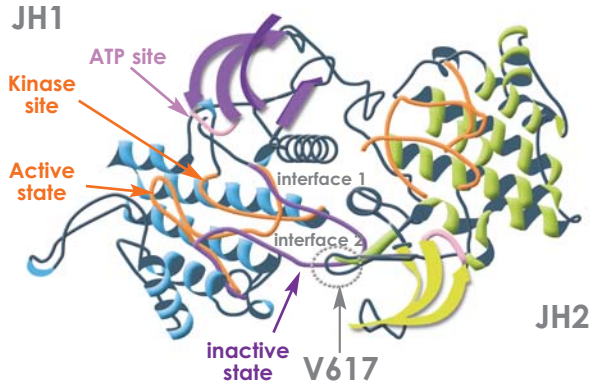


JAK2 V617F - Positive Myeloproliferative Disorders

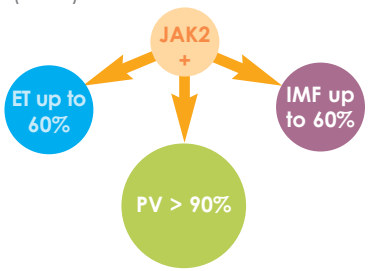
■ Recently, several groups reported a single, acquired point mutation (1849G>T) in the Janus kinase 2 (JAK2) gene in the majority of patients with Ph-negative myeloproliferative disorders. This somatic mutation causes the substitution of phenylalanine for valine at position 617 of the JAK2 (p.Val617Phe or V617F).



■ JAK2 V617F protein binds the intra-cytoplasmic sequences of multiple cytokine receptors via their FERM domain. The V617F mutation in JAK2 is located in the JH2, or pseudokinase domain, which negatively regulates the kinase domain (JH1). Biochemical studies have shown that the JAK2 V617F mutation causes cytokine-independent proliferation of cell lines that express erythropoietin receptors and leads these cells to become hypersensitive to cytokines.

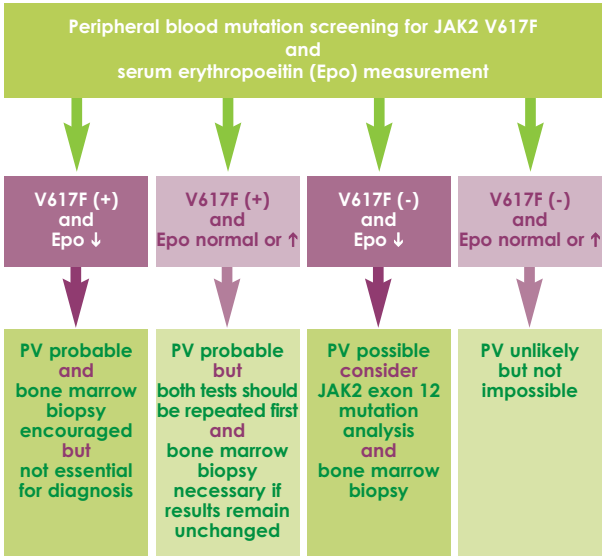


■ JAK2 V617F has been identified in more than 90% of patients with polycythaemia vera and in 50% to 60% of patients with essential thrombocythaemia or idiopathic myelofibrosis. This mutation has also been observed in several related leukaemic disorders, including chronic neutrophilic leukaemia, chronic eosinophilic leukaemia, chronic myelomonocytic leukaemia (CMML), and rare cases of myelodysplastics syndromes (MDS).



Clinical Utility of Direct Diagnostic Test for the JAK2 V617F mutation

■ **To confirm a diagnosis of PV, ET, and IMF:**
Genetic test-based diagnostic algorithm for suspected polycythaemia vera (PV) :



**from Tefferi A & Pardanani A.*

■ **To confirm essential thrombocythaemia (ET)** with a persistent thrombocytosis > 450 x 10⁹/L in the absence of an alternative cause. However, ET must be differentiated from another MPD, chronic