CPAL
Central **P**ennsylvania **A**lliance **L**aboratory

Technical Bulletin
No. 100

August 2, 2012

JAK2 AND MPL 515 MUTATIONAL ANALYSIS

Contact:
Dr. Jeffrey Wisotzkey, 717-851-1422
Technical Director, CPAL

Jill A. Johns, MT(ASCP)SH, 717-851-4320
Operations Manager, Flow Cytometry and Molecular Diagnostics

Performed:
Typically set up Monday through Friday. The testing schedule may be adjusted week to week to maximize workflow efficiencies. Expected Turn-Around-Time (TAT) is 1-3 days from receipt of specimens at CPAL.

Ordering:
Each assay may be ordered individually (JAK2 V617F, MPL515, JAK2 Exon 12) or reflex testing may be ordered.

Mnemonics:
JAK2 orders the JAK2 V617F quantitative mutation assay
MPL515 orders the MPL 515 qualitative mutation assay
Exon 12 orders the JAK2 exon 12 assay
JAK2PLUS orders JAK2. If the JAK2 V617F result is negative, then the Exon 12 assay is performed.
MPN orders the JAK2. If the JAK2 V617F result is negative, then the Exon 12 assay is performed. If the Exon 12 assay is negative, then the MPL515 assay is performed.

Method: JAK2: Quantitative real time PCR
MPL 515: Qualitative real time PCR
JAK2 Exon 12: DNA (Sanger) Sequencing

Clinical Use:

- Individuals suspected of having polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (MF).
- *JAK2* V617F mutation-positive individuals undergoing treatment for PV, ET, or MF.

Specimen: Peripheral Blood or Bone Marrow (EDTA)

Reference Ranges:

Not Detected

Summary:

Chronic myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell malignancies characterized by excessive production of blood cells. ET, MF, and PV are the 3 most common *BCR/ABL*-negative MPNs and are associated with thrombosis and hemorrhage, splenomegaly, and the risk of transformation to acute myeloid leukemia.

Diagnostic criteria for ET, MF, and PV adopted by the World Health Organization (WHO) include identification of a clonal marker, with a specific recommendation to test for the *JAK2* V617F mutation in exon 14.[1] *JAK2* V617F is a gain-of-function mutation that leads to clonal proliferation; it is present in about 95% of PV cases and about half of ET and MF cases. The *JAK2* allele burden decreases with successful therapy, disappears in some patients, and reappears during relapse.[2,3] Thus, quantitative *JAK2* analysis may be useful for diagnosis and patient management. In *JAK2* V617F-negative patients, the presence of a *JAK2* exon 12 mutation also meets the WHO criterion for establishing clonality. Exon 12 mutations have been found in patients with PV who present with erythrocytosis but are typically not associated with ET or MF.[4,5]

Because a significant proportion of patients with ET or MF are negative for *JAK2* mutations, other somatic mutations were sought; hence mutations in the myeloproliferative leukemia gene (*MPL*) were identified.[8] *MPL*, found at chromosome 1p34, encodes the thrombopoietin receptor that works in concert with thrombopoietin for platelet production. Acquired *MPL* mutations (eg, W515L and W515K) are associated with severe anemia and have been detected in patients with ET or MF but not in patients with PV[6,7] An inherited *MPL* mutation (S505N; exon 10) has also been found in a Japanese pedigree with familial ET.[8] (MPL S505N Mutational analysis is not performed at CPAL.

For diagnostic purposes, test selection is best based on the hematologic characteristics and relative prevalence of *JAK2* and *MPL* mutations in patients with *BCR/ABL*-negative MPNs. Typically, mutations in *MPL* and *JAK2* exon 12 are investigated after the *JAK2* V617F mutation has been ruled out.

The presence of a *JAK2* V617F or exon 12 mutation is consistent with the diagnosis of PV. *JAK2* V617F-positive results may also be associated with ET, MF, or, rarely, with other myeloid neoplasms.[1] In patients with suspected ET or MF, a *JAK2* V617F-positive result rules out reactive thrombocytosis and myelofibrosis.[1] A negative result does not rule out the diagnosis of PV, ET, or MF. When monitoring disease, a decrease in *JAK2* V617F concentration suggests therapeutic response; an increase suggests relapse.

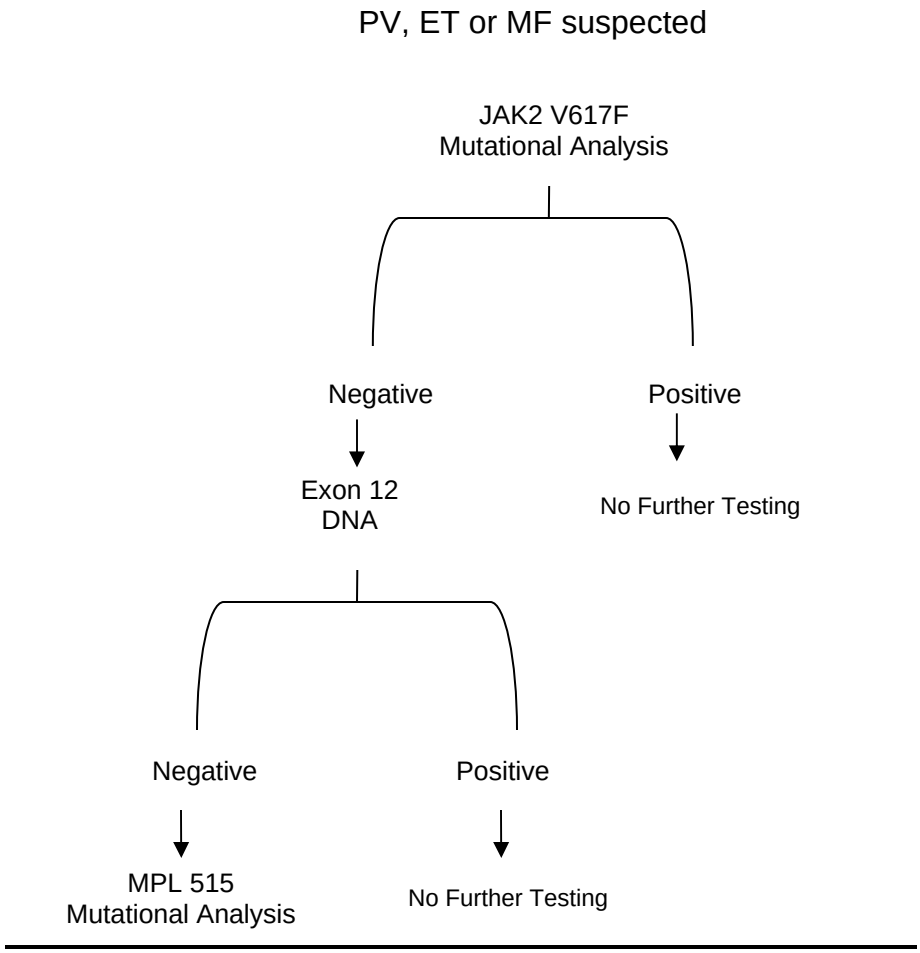
The presence of a *MPL* W515 mutation is consistent with ET or MF and meets the WHO diagnostic criterion for establishing clonality; *MPL* S505N is consistent with familial ET. A negative finding does not rule out ET or MF.

These assays detect mutations only in the exons tested; polymorphisms or mutations at other locations will not be detected. Test results should be interpreted in conjunction with other laboratory and clinical findings. False-negative results may occur when there is a low mutant allele burden in the peripheral blood.

Myeloproliferative Neoplasms

Disease	GENETIC MUTATION	FREQUENCY (%)
CML	BCR/ABL	100
ET	JAK2 V617F	50
	MPL 515	1
PMF	JAK2 V617F	50
	MPL 515	5-7
PV	JAK2 V617F	>95
	JAK2 EXON 12	2-4

CML, chronic mylogenous leukemia; **ET**, essential thrombocythemia; **PMF**, primary myelofibrosis; **PV**, polycythemia vera



Limitations of Procedure:

References:

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4. Scott LM, Tong W, Levine RL, et al. *JAK2* exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med.* 2007;356:459-468.

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