CALR (Calreticulin) Exon 9 Mutation Detection

Effective Date: January 09, 2017 **Performing Department:** Molecular Pathology

Clinical Significance:

Myeloproliferative neoplasms (MPNs) are clonal myeloid-cell derived disorders characterized by expansion of mature peripheral blood cell populations such as granulocytes, red blood cells and/or platelets. Typically, patients also show bone marrow hypercellularity and have a predisposition to thrombosis, hemorrhage, and/or marrow fibrosis. Classic myeloproliferative neoplasms are negative for the *BCR/ABL* translocation and do not include chronic myelogenous leukemia (CML). These are: polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocythemia (ET). A single point mutation, *JAK2* V617F, is present in the majority of PV cases, and is also detectable in approximately 50% and 40-50% of PMF and ET cases, respectively. The recent discovery of this mutation and rapid translation of testing into clinical practice has significantly streamlined the diagnosis of MPNs. Because of the high percentage of *JAK2* V617F positive classic MPN cases, testing for this mutation should always be performed first when evaluating a possible case of MPN. However, there are now additional mutations known to be associated with *JAK2* V617F-negative, classic MPN categories PMF and ET. One is mutation in the calreticulin gene, *CALR*. Mutations in CALR have been found in about 70% patients with *JAK2*-negative essential thrombocythemia (ET), and 60-85% in *JAK2*-negative primary myelofibrosis. The detection of a *CALR* mutation may aid in the diagnosis of a myeloproliferative neoplasm by helping to distinguish clonal, neoplastic disease from a benign reactive process. In addition, MPN patients with a *CALR* mutation have a more indolent disease course, a lower thrombotic risk, and longer overall survival as compared to those with a *JAK2* mutation. So-called triple-negative patients (nonmutated *JAK2*, *CALR*, and another gene, *MPL*) carry a poor prognosis and demonstrate a high rate of leukemic transformation in some studies.

CALR mutations are small deletions and insertions in exon 9 of the gene. The most common are Type I (52-bp deletion, c.1092_1143del,p.L367fs*46) and Type II (5-bp insertion, c.1154_1155insTTGCC, p.K385fs*47) mutations. These are found in 53% and 32% of all MPN cases with mutant *CALR*.

Use:

- Assist with diagnostic confirmation and classification of myeloproliferative neoplasia
- Clarify the distinction between a reactive cytosis and a myeloproliferative neoplasm
- Provide prognostic information regarding myeloproliferative neoplasia to assist with treatment planning

Method:

Polymerase Chain Reaction (PCR) amplification of mutation specific targets followed by capillary electrophoresis (fragment analysis).

Reference Values

Negative: No mutation detected

Positive: Mutation detected

Interpretive Information:

This test is designed to detected mutations in exon 9 of the CALR gene only. The limit of detection for this test is approximately 5% mutant allele.

Mutations in other locations within the *CALR* gene or mutations in other genes will not be detected.

Results of this test must be interpreted in the context of other clinical data. A positive result does not constitute a diagnosis of myeloproliferative neoplasm or other malignancy.

Specimen Requirement and Collection:

Collect: Whole blood (5mL) or bone marrow (3mL) in an EDTA anticoagulated tube (lavender top tube)

Specimen Preparation: Do not freeze. Transport 5 mL whole blood. (Min: 1 mL) or Transport 3 mL bone marrow. (Min: 1mL)

Storage/Transport Temperature: Refrigerated up to 10 days

Unacceptable Condition: Serum/plasma only; specimens collected in anticoagulants other than EDTA; grossly clotted or hemolyzed specimens; frozen specimens

Stability: Ambient: 24 hours; Refrigerated: 10 days; Frozen: Unacceptable

Day Run: Monday

Time Run: 9AM

Time Reported: Within 24 hours of run

TAT: 2-7 Days

Test Type: GENETIC

Order: 36053

CPT Code: 81219

Related Tests

Test Code	Test Name
36140	JAK2 (V617F) Mutation Analysis
36054	MPL Exon 10 Codon 515 Mutation Detection
36052	Myeloproliferative Neoplasia Cascade: *JAK2* (V617F) Mutation Analysis. When negative, *CALR* (Calreticulin) Exon 9 Mutation detection will be performed. When this is negative, MPL codon 515 Mutation Detection test will be performed

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