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*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Description

Mutations in the gene encoding Janus kinase 2 (JAK2) protein and in the myeloproliferative leukemia virus oncogene (MPL) encoding the thrombopoietin receptor have been associated with myeloproliferative neoplasms and with acute lymphoblastic leukemia (ALL) in Down syndrome patients. This Protocol addresses the use of JAK2 and MPL gene mutation testing for diagnosis, prognosis, and treatment selection in patients with myeloproliferative neoplasms. This Protocol also will address the potential use of JAK2 mutations in the diagnosis or selection of treatment in patients with Down syndrome and acute lymphoblastic leukemia.

Background

Myeloproliferative neoplasms (MPNs) are uncommon overlapping blood diseases characterized by the production of one or more blood cells and includes chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), systemic mastocytosis, chronic eosinophilic leukemia, and others. A common finding in many of the MPNs is clonality, and a central pathogenic feature is the presence of a mutated version of the tyrosine kinase enzyme, such that it is abnormally constitutively activated. The paradigm for use of this information to revolutionize patient management is CML. A unique chromosomal change (the Philadelphia chromosome) and an accompanying unique gene rearrangement (BCR-ABL) resulting in a continuously activated tyrosine kinase enzyme were identified. These findings led to the development of targeted tyrosine kinase inhibitor drug therapy (imatinib) that produces long-lasting remissions.

Diagnosis and monitoring of patients with Philadelphia chromosome-negative MPNs have been challenging because many of the laboratory and clinical features of the classic forms of these diseases – PV, ET, and PMF – can be mimicked by other conditions such as reactive or secondary erythrocytosis, thrombocytosis, or myeloid fibrosis. In addition, these entities can be difficult to distinguish on morphologic bone marrow exam, and diagnosis can be complicated by changing disease patterns: PV and ET can evolve into PMF or undergo leukemic transformation. World Health Organization (WHO) criteria were published as a benchmark for diagnosis in 2001. These have been challenging to use because they involve complex diagnostic algorithms, rely on morphologic assessment of uncertain consistency, and require tests that are not well-standardized or widely available, such as endogenous erythroid colony formation.

In March and April of 2005, four separate groups using different modes of discovery and different measurement techniques reported the presence of a novel somatic point mutation in the conserved autoinhibitory pseudokinase domain of the gene encoding JAK2 protein in patients with classic MPNs. The mutation was noted to cause a valine-to-phenylalanine substitution at amino acid position 617 (JAK2^{V617F}). Loss of JAK2 autoinhibition, caused by JAK2^{V617F}, results in constitutive activation of the kinase and in recruitment and phosphorylation of substrate molecules including signal transducers and activators of transcript (STAT) proteins

(so-called JAK-Stat signaling). The result is cell proliferation independent of normal growth factor control. These findings were subsequently confirmed, and additional mutations affecting the *JAK2* gene – mutations in exon 12 or in complementary pathways such as thrombopoietin-receptor-pathway mutations in *MPL* exon 10 – were identified. These mutations were seen with varying but reliable frequency in patients with classic MPNs and with uncommon and erratic frequency in other MPNs. In addition, unique cases of *JAK2* mutations were reported in a subset of patients with Down syndrome-associated acute lymphoblastic leukemia (ALL).

Although these mutations were of importance in better understanding the biology of MPNs, they also were of immediate interest as laboratory tools to aid in diagnosis and management of disease. To that end, at least four potential intended uses for mutation testing have been considered, including:

- a. Diagnosis of patients with clinical, laboratory, or pathologic findings suggesting classic MPNs (PV, ET, or PMF);
- b. Diagnosis or selection of treatment for patients with Down syndrome ALL;
- c. Phenotyping of disease subtypes in patients with MPNs to establish disease prognosis;
- d. Identification, selection, and monitoring of treatment.

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *JAK2* testing and *MPL* mutation testing. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests. Variable analytic and clinical performance has been reported, suggesting that nucleic acid amplification methodologies are more sensitive than mutation sequence analysis. It appears that there can be considerable interassay and interlaboratory variability in the generation of testing results.

Policy (Formerly Corporate Medical Guideline)

JAK2 tyrosine kinase and *MPL* mutation testing may be considered **medically necessary** in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting classic forms of myeloproliferative neoplasms (MPN), that is, polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF).

JAK2 tyrosine kinase and *MPL* mutation testing may be considered **investigational** in all other circumstances including, but not limited to, the following situations:

- Diagnosis of nonclassic forms of MPNs
- Molecular phenotyping of patients with MPNs
- Monitoring, management, or selecting treatment in patients with MPNs
- Diagnosis or selection of treatment in patients with Down syndrome and acute lymphoblastic leukemia

Policy Guideline

Testing strategy

Patients suspected to have polycythemia vera (PV) should first be tested for the most common finding *JAK2*^{V617F}. If testing is negative, further testing to detect other *JAK2* tyrosine kinase mutations, e.g., in exon 12, is warranted.

Patients suspected to have essential thrombocythemia (ET) or primary myelofibrosis (PMF) should first be tested for *JAK2* mutations, as noted. If testing is negative, further testing to detect *MPL* mutations is warranted.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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