Template for Reporting Results of Biomarker Testing for Myeloproliferative Neoplasms

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This biomarker template is NOT required for accreditation purposes

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With guidance from the CAP Cancer Biomarker Reporting Committee

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Summary of Changes

Added note:

All cytogenetic variations should be reported using the International System for Human Cytogenetic Nomenclature (ISCN) and gene sequence variations should be reported following the recommendations of the Human Genome Variation Society (http://varnomen.hgvs.org/; accessed May 9, 2017).

MPN Biomarker Reporting Template

Template web posting date: June 2017

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient's medical record and thus readily available to the treating clinical team. **This template is not required for accreditation purposes.**

MYELOPROLIFERATIVE NEOPLASMS (MPNs)

Select a single response unless otherwise indicated.

Note: *Use of this template is optional.*

+ SPECIMEN TYPE
+ ___ Peripheral blood
+ ___ Bone marrow
+ ___ Isolated granulocytes from peripheral blood
+ ___ Other (specify): _____

+ RESULTS

Note: If a marker is tested by more than one method (eg, polymerase chain reaction and immunohistochemistry), please document the additional result(s) and method(s) in the Comments section of the report.

+ Cytogenetic Testing Results (karyotype)
+ ___ No abnormalities detected
+ ___ Abnormal karyotype detected (specify): _____

+ Fluorescence In Situ Hybridization (FISH) Testing (select all that apply)
+ ___ *BCR-ABL1*
    + ___ No *BCR-ABL1* fusion detected
    + ___ *BCR-ABL1* fusion detected (specify percent positive cells): _____%
+ ___ *PDGFRA*
    + ___ No *PDGFRA* fusion detected
    + ___ *FIP1L1-PDGFRA* fusion detected (specify percent positive cells): _____%
    + ___ Other *PDGFRA* fusion detected (specify percent positive cells): _____%
+ ___ *PDGFRB*
    + ___ No *PDGFRB* fusion detected
    + ___ *ETV6-PDGFRB* fusion detected (specify percent positive cells): _____%
    + ___ Other *PDGFRB* fusion detected (specify percent positive cells): _____%
+ ___ *FGFR1*
    + ___ No *FGFR1* rearrangement detected
    + ___ *FGFR1* rearrangement detected (specify percent positive cells): _____%

+ *BCR-ABL1* Transcript Reverse Transcription Polymerase Chain Reaction (RT-PCR) Testing
+ ___ No *BCR-ABL1* fusions detected
+ ___ *BCR-ABL1* fusions detected
    If quantitative testing performed:
    + *BCR-ABL1* normalized copy number (*BCR-ABL1*/reference gene): _____
    + Percent *BCR-ABL1* on international scale (e13/14a2 (p210) fusions only): _____%

+ *JAK2* p.V617F (c. 1849G>T) Mutation Testing
+ ___ No mutation detected
+ ___ Mutation detected

    + For *JAK2* p.V617F, if test is quantitative, specify quantitative value: _____
        Reported as:
        + ___ Percent mutant allele burden
        + ___ Percent transcript levels
        + ___ Normalized copy number (V617F transcripts/reference gene)

+ Additional Mutation Testing (select all that apply)
+ ___ *JAK2* exon 12
    + ___ No *JAK2* exon 12 mutation detected
    + ___ *JAK2* exon 12 mutation detected (specify mutation): _____
+ ___ *MPL*
    + ___ No *MPL* mutation detected
    + ___ *MPL* mutation detected (specify mutation): _____
+ ___ *CALR* (calreticulin)
    + ___ No *CALR* mutation detected
    + ___ *CALR* mutation detected (specify mutation): _____
+ ___ *KIT*
    + ___ No *KIT* mutation detected
    + ___ *KIT* mutation detected (specify mutation): _____
+ ___ Other (specify gene): _____
    + ___ No mutation detected
    + ___ Mutation detected (specify mutation): _____

+ METHODS

+ *BCR-ABL1* Transcript RT-PCR Testing
    + *BCR-ABL1* RT-PCR assay sensitivity: _____

+ *JAK2* p.V617F (c. 1849G>T*)* Mutation Testing
    + Assay sensitivity: _____
    + Assay method:
        + ___ Allele-specific PCR
        + ___ Sanger sequencing
        + ___ Pyrosequencing
        + ___ Next-generation sequencing
        + ___ Other (specify): _____

+ Other Mutation Testing (specify gene): _____
+ Assay sensitivity: _____
+ Assay method:
+ ___ Allele-specific PCR
+ ___ Sanger sequencing
+ ___ Pyrosequencing
+ ___ Next-generation sequencing
+ ___ Other (specify): _____
+ Exon(s)/codon(s) covered: _____

+ COMMENT(S)

_____
_____

Gene names should follow recommendations of The Human Genome Organisation (HUGO) Nomenclature Committee (www.genenames.org; accessed February 10, 2015).

All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (www.hgvs.org/mutnomen/; accessed February 10, 2015).

All cytogenetic variations should be reported using the International System for Human Cytogenetic Nomenclature (ISCN) and gene sequence variations should be reported following the recommendations of the Human Genome Variation Society (http://varnomen.hgvs.org/; accessed May 9, 2017).

Explanatory Notes

Myeloproliferative neoplasms (MPNs) are clonal disorders characterized by the expansion of one or more myeloid lineages leading to increased bone marrow cellularity and elevated peripheral blood myeloid cell counts. The latter may manifest as granulocytosis, erythrocytosis, thrombocytosis, or a combination, depending on the disease subtype. The diagnosis and classification of MPNs require synthesis of the clinical, morphologic, immunophenotypic, and molecular genetic findings. Over the course of the last few years, the spectrum of genetic mutations identified in MPNs has expanded, and polymerase chain reaction (PCR) and/or sequence-based mutation testing is now routinely incorporated into the diagnostic workup. However, the diagnosis still relies heavily on the peripheral blood and bone marrow morphologic findings and the clinical features of the disease, particularly for those patients who do not have a disease-defining genetic abnormality.

In the 2008 World Heath Organization (WHO) classification system, the category of MPNs includes chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia, NOS, mastocytosis, and myeloproliferative neoplasm, unclassifiable (MPN-U), and the clinical and pathologic findings may overlap with the category of myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB,* and *FGFR1*.[1] Classical cytogenetic karyotyping and fluorescence in situ hybridization (FISH) testing are often used in the evaluation of patients to test for the presence of t(9;22)(q34;q11.2);*BCR-ABL1*, particularly for those who present with neutrophilic leukocytosis, and for abnormalities of *PDGFRA*, *PDGFRB* and *FGFR1* for those patients who present with eosinophilia. Otherwise, patients with MPNs may have a variety of cytogenetic abnormalities. Various trisomies such as +8 and/or +9 are often identified. Given the degree of standardization and specialization that has occurred in *BCR-ABL1* testing, and the repeated nature of the analyses, the College of American Pathologists (CAP) has published a separate CML monitoring template for those patients known to have CML.

When the cytogenetic and/or FISH testing results are nonspecific or negative, it may be necessary to utilize additional molecular genetic tests. The *JAK2* p.V617F (c.1849G>T) somatic point mutation is present in almost all patients with PV and in a large proportion (40%-50%) of patients with ET or PMF. Both qualitative and quantitative testing methods are employed, although the utility of quantitation of the mutant *JAK2* allele burden remains somewhat controversial. A small percentage of patients with PV who lack evidence of a *JAK2* p.V617F mutation may have a mutation in exon 12 of *JAK2,* and these are often insertions or deletions.[2] Different testing methods are often utilized for *JAK2* p.V617F and *JAK2* exon 12 mutations, and it should be noted that different methods, for example Sanger sequencing and allele-specific PCR, may have markedly different sensitivities. Mutations in the *CALR* (calreticulin) gene were recently identified in the majority of patients with ET or PMF who lack *JAK2* mutations.[3,4] Less commonly, mutations in the MPL gene are present in a subset of ET/PMF patients without *JAK2* or *CALR* mutations.[3,] *KIT* mutation testing is helpful for the diagnosis and subclassification of mastocytosis and is important for determining the likely response to tyrosine kinase inhibitor (TKI) therapy.[5]

Given the pace of recent findings, additional pathologically relevant mutations are likely to be identified and/or clinically validated in the near future. With this in mind, the template includes space for reporting other mutation testing, and future template updates will reflect additional molecular genetic findings that may be incorporated into the WHO classification system.

References

1. Swerdlow SH, Campo E, Harris NL, et al. *World Health Organization Classification of Tumours of Hematopoietic and Lymphoid Tissues.* Lyon, France: IARC; 2008.
2. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *New Engl J Med*. 2007;356:459-468.
3. Klampfl T, Gissinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *New Engl J Med.* 2013;369:2379-2390.
4. Nangalia J, Massie CE, Baxter EJ, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *New Engl J Med.* 2013;369:2391-2405.

5. Ma Y, Zeng S, Metcalfe DD, et al. The c-KIT mutation causing human mastocytosis is resistant to STI571 and other KIT kinase inhibitors; kinases with enzymatic site mutations show different inhibitor sensitivity profiles than wild-type kinases and those with regulatory-type mutations. *Blood*. 2002;99:1741-1744.