UNC Myeloid Mutation Panel: For Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS), or Myeloproliferative neoplasms (MPN)

The UNC Molecular Genetics Laboratory performs a myeloid mutation panel targeting selected regions of multiple genes using next-generation sequencing to facilitate disease classification and to guide selection of therapy.

Rationale for testing:
Testing for the presence of somatic gene mutations may assist in diagnosis, prognosis, and therapy selection for myeloid disorders. All regions listed are analyzed in both the AML and MDS/MPN panel. The AML panel includes FLT3-ITD/TKD testing and RNA extraction for possible quantitative NPM1 testing.

1) **AML:** Mutational information impacts World Health Organization classification and prognosis in AML. For instance, AML with NPM1 mutation or biallelic CEBPA mutation are recognized as distinct entities, which generally have favorable prognosis. To identify patients who may benefit from targeted therapy with midostaurin, a separate FLT3-ITD/TKD panel is included with this order. For specimens that test positive for NPM1 mutation, the NPM1 Q-rtPCR assay will be ordered to determine whether that test may be used for minimal residual disease (MRD) monitoring.

2) **MDS:** The presence of a somatic mutation may assist diagnosis by supporting the presence of a clonal process. In patients with confirmed MDS, SF3B1 mutation may confer a favorable prognosis, whereas mutation in ASXL1, BCOR, CBL, ETV6, EZH2, NRAS, PPM1D, RUNX1, SETBP1, SRSF2, STAG2, TP53, or U2AF1 is associated with less favorable outcome.

3) **MPN:** The presence of a somatic mutation may assist diagnosis by supporting the presence of a clonal process. In addition, many BCR-ABL1-negative MPNs are associated with characteristics mutations, such as JAK2 mutation polycythemia vera, JAK/CALR/MPL mutation in essential thrombocythemia and primary myelofibrosis, and CSF3R mutation chronic neutrophilic leukemia. Mutations in additional genes on this panel have prognostic significance in MPNs.

Clinical Indications for Myeloid Mutation Panel testing:
1) **For AML:** Refine classification and prognosis.
2) **For MDS:** Demonstrate clonality to assist in diagnosis and refine prognosis.
3) **For MPN:** Assist in diagnosis and prognosis of polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic neutrophilic leukemia, and other BCR-ABL1-negative MPNs.

Specimen Requirements for the Myeloid Mutation Panel:
Bone marrow aspirate (1 mL, EDTA) or peripheral blood (3mL, EDTA) having at least 30% myeloid cells, and refrigerated for up to 72 hours. Unacceptable sample types include: fresh, frozen, or paraffin embedded tissue. The assay is sensitive to variants above 5% allele frequency (10% clonal cells). This test is NOT appropriate for MRD monitoring. For patients undergoing repeat testing, previously detected variants will be reported to 3% VAF.

Gene Regions Tested – These regions are covered by both the AML and MDS/MPN Panel

- **ABL1 (exons 4-9)**
- **ASXL1 (exons 8-12)**
- **BCOR (exons 2-15)**
- **BRAF (exon 15)**
- **CALR (exon 9)**
- **CBL (exons 8,9)**
- **CEBPA (full coverage)**
- **CSF3R (exons 4-17)**
- **DNMT3A (all exons)**
- **ETV6 (all exons)**
- **EZH2 (all exons)**
- **FLT3 (exons 13,14,15,20)**
- **HRAS (exons 2,3)**
- **IDH1 (exon 4)**
- **IDH2 (exons 4,5)**
- **JAK2 (all exons)**
- **KIT (exons 2,8-13,17-19)**
- **KRAS (exons 2,3)**
- **MPL (exon 10)**
- **MYD88 (all exons)**
- **NOTCH1 (all exons)**
- **NPM1 (exons 11,12)**
- **NRAS (exons 2,3)**
- **PPM1D (all exons)**
- **PTPN11 (exons 3, 7-13)**
- **RUNX1 (all exons)**
- **SETBP1 (exon 4)**
- **SF3B1 (exons 10-16)**
- **SRSF2 exons (all exons)**
- **STAG2 (all exons)**
- **TET2 (all exons)**
- **TP53 (all exons)**
- **U2AF1 (exons 2,6)**
- **WT1 (exons 6-10)**
- **ZRSR2 (all exons)**

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Limitations:
Gene amplifications, translocations, and insertions or deletions over 90 bases in length are not reliably detected by this assay. Variants predicted to be non-deleterious (such as synonymous coding changes and population variants) are not reported. Lack of mutation does not exclude myeloid neoplasia. Presence of clonality does not establish a diagnosis of malignancy. Normal tissue is not tested to determine whether a gene variant is somatic (acquired) or germline (heritable). If the patient has evidence of a heritable cancer syndrome (e.g. different tumor types, early age of onset, family history), genetic counseling is recommended.

References:

Questions?
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