MYELOPROLIFERATIVE NEOPLASMS

Next Generation Sequencing Mutation Analysis

Experience.
MPLN

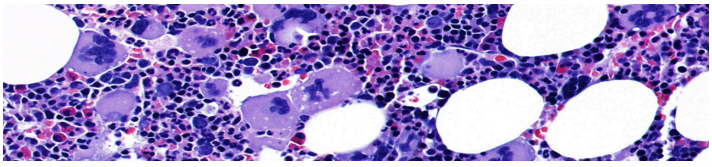
Clinical data and practice guidelines have evolved at a rapid pace for this heterogeneous group of disorders. To date, conventional approaches to mutation profiling have involved complex, sequentially cascaded testing algorithms that are resource intensive and often inefficient. With the advent of next generation sequencing (NGS), multiplex targeted gene panels now provide a practical solution for comprehensive mutation analysis in routine clinical practice.

Evidence Based Laboratory Medicine

MPLN NGS panel content is based on NCCN and updated WHO practice guidelines.[1,2] Peripheral blood is an acceptable specimen to screen for mutations in MPNs, including JAK2, CALR, and/or MPL. Oncogenic driver mutations significantly impact prognosis and management in MPNs[3], and mutations may also serve as diagnostically useful markers of clonality. For example, the differential diagnosis of chronic eosinophilic leukemia, not otherwise specified (CEL, NOS) and idiopathic hypereosinophilic syndrome is known to be especially challenging, as the former generally requires identification of clonal cytogenetic abnormalities that are only rarely detected. In a recent study involving the nation's leading cancer centers, the diagnosis of CEL, NOS was initially missed in ~1/3 of patients, however utilization of NGS mutation data resulted in accurate reclassification of these cases.[4] NGS panel testing also informs prognostic risk stratification in PMF, where survival has been reported to broadly range from 3.2 - 17.7 years, depending on mutation subtype.[5] Additional clinically relevant applications are indicated on right.

Ordering Requirements

Turnaround Time	7-10 days
Specimen Requirements	5 mL whole blood or 3mL bone marrow (EDTA or Heparin)
Storage and Handling	Transport at ambient temperature (18-25°C)



Clinically Relevant Mutations

PANEL CONTENT

MPN CORE PANEL

JAK2 (V617F and Exon 12), CALR, MPL

MYELOID EXTENDED PANEL

JAK2 (V617F and Exon 12), CALR, MPL, ASXL1, CBL, CSF3R, ETV6/TEL, EZH2, IDH1, IDH2, KIT, KRAS, NRAS, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53

DIAGNOSIS

POLYCYTHEMIA VERA

JAK2 (V617F) is present in >95% of cases. JAK2 exon 12 mutant PV comprises the remainder of cases.

PRIMARY MYELOFIBROSIS, ESSENTIAL THROMBOCYTHEMIA

JAK2 (V617F), CALR, and MPL mutations are mutually exclusive and occur in ~50-60%, 25%, and 5% of cases, respectively.

ATYPICAL CHRONIC MYELOGENOUS LEUKEMIA

SETBP1 mutations occur in approximately 30% of cases.

CHRONIC NEUTROPHILIC LEUKEMIA

CSF3R activating mutations are now a primary diagnostic criterion.

CHRONIC MYELOMONOCYTIC LEUKEMIA

TET2, SRSF2, ASXL1, CBL, SETBP1, KRAS, NRAS, and/or EZH2 pathogenic mutations occur in >80% of cases.

PROGNOSIS

PRIMARY MYELOFIBROSIS (PMF)

Triple-negative PMF and CALR-mutant PMF have been associated with overall survival ranging from 3.2 to 17.7 years, respectively.

ASXL1, EZH2, IDH1/2, and SRSF2 mutations independently predict inferior leukemia free survival.

ESSENTIAL THROMBOCYTHEMIA (ET)

Triple-negative mutation status is favorable and predicts lower incidence of vascular events, the primary complication of ET

References

1. Arber et al. (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 127(20):2391-405.
2. Myeloproliferative Neoplasms, Clinical Practice Guidelines in Oncology (V.2.2017) National Comprehensive Cancer Center Network.
3. Rumi et al. (2017) Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms. Blood. 129(6): 680-692
4. Wang et al. (2016) Targeted next-generation sequencing identifies a subset of idiopathic hypereosinophilic syndrome with features similar to chronic eosinophilic leukemia, not otherwise specified. Mod Pathol. 29(8):854-64.
5. Rumi E et al. (2014) Clinical effect of driver mutations of JAK2, CALR, or MPL in primary myelofibrosis. Blood. 14; 124:1062

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