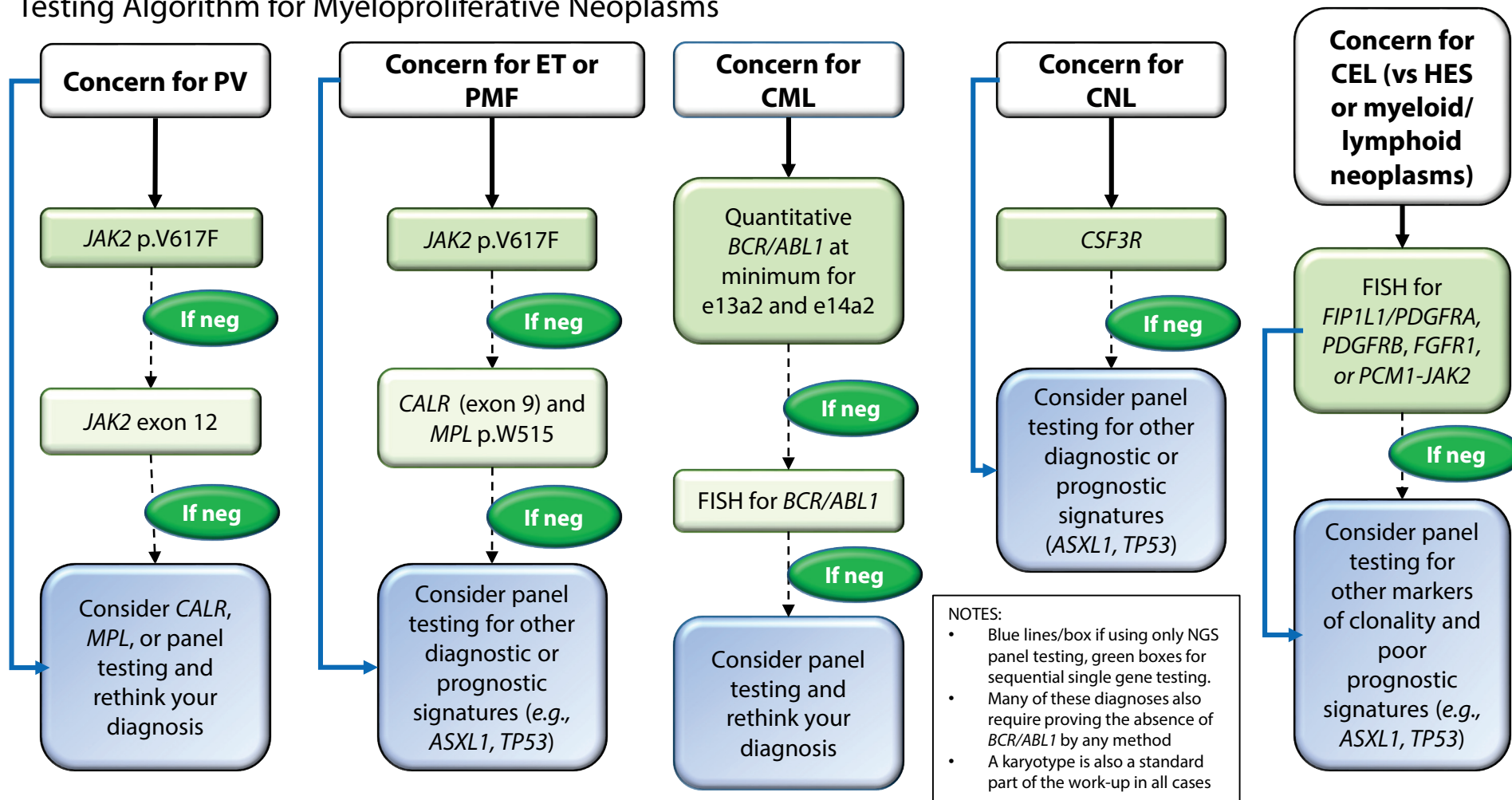


ONCOLOGY: Myeloproliferative Neoplasms

Testing Algorithm for Myeloproliferative Neoplasms



Abbreviations: PV – Polycythemia Vera; ET – Essential Thrombocythemia; PMF – Primary Myelofibrosis; CML – Chronic Myeloid Leukemia; CNL – Chronic Neutrophilic Leukemia; CEL – Chronic Eosinophilic Leukemia; HES – hypereosinophilic syndrome; MPN – myeloproliferative neoplasm; MDS – myelodysplastic syndrome; RS – ring sideroblast; T – thrombocytosis; VAF – variant allele frequency

Genes to Test in Myeloproliferative Neoplasms

Samples to Test: Peripheral Blood or Bone Marrow **Abbreviations:** See Opposite Side of Card

Biomarker	Specific Alterations/ Alternative Terms	Indications	Result Interpretation/Significance
<i>BCR/ABL1</i>	Philadelphia (Ph) Chromosome Usually p210 fusions - e13a2 and e14a2 Rarely p190 fusion - e1a2 or p230 fusion - e19a2 or fusions involving a3	Diagnosis and monitoring of CML Diagnosis of other MPNs and MDS/MPNs which require exclusion of CML by negative <i>BCR/ABL1</i> Therapy: ABL1 kinase inhibitors	Diagnostic of CML in the correct clinical context. Also found in some ALLs and AMLs. Reported in International Scale (% IS), used for monitoring CML
<i>JAK2</i>	p.V617F activating hotspot Exon 12 activating substitution mutations	Diagnosis: p.V617F for first line single gene testing for PV (95%), ET (50-70%), and PMF (30-50%) Exon 12 mutations (~5% of PV) Therapy: JAK2 inhibitors	p.V617F not specific for a single disease can be found in a wide range of myeloid neoplasms, associated with thrombosis and erythrocytosis High VAF (>75%) is associated with disease progression
<i>CALR</i>	Exon 9 frameshift mutations	Diagnosis: <i>CALR</i> exon 9 frameshift in ET (25-30%) and PMF (30-35%)	Exon 9 frameshift not specific for a single disease but are useful to support a diagnosis of ET or PMF
<i>MPL</i>	p.W515K/L activating hotspot	Diagnosis: <i>MPL</i> p.W515K/L in ET (5%) and PMF (5-10%)	p.W515K/L not specific for a single disease but are useful to support a diagnosis of ET or PMF
<i>CSF3R</i>	p.T618I activating hotspot Other activating substitutions, predominantly exon 17	Diagnosis: CNL (100%), other myeloid neoplasms Therapy: p.T618I - possible ruxolitinib sensitivity p.S783fs* - possible dasatinib sensitivity	Mutated in nearly all cases of CNL as well as in other myeloid neoplasms Specific mutations suggest therapy
<i>FIP1L1/PDGFRB</i>	Usually cryptic deletion involving <i>CHIC2</i>	Diagnosis: identify specific subtype of neoplasms Therapy response: <i>PDGFRB</i> fusions are typically responsive to kinase inhibitors such as imatinib <i>FGFR1</i> fusions are typically non-responsive to imatinib and may need newer agents	Fusions involving <i>PDGFRB</i> , <i>FGFR1</i> , and <i>JAK2</i> are diagnostic of a specific subgroup of lymphoid and myeloid neoplasms with eosinophilia that are considered in a distinct category from MPNs, but may be considered in the differential of CEL
<i>PDGFRB</i> /various partners	Various fusion partners, most commonly <i>ETV6</i>		
<i>FGFR1</i> /various partners	Various fusion partners		
<i>PCM1-JAK2</i>	Also includes other partners of <i>JAK2</i> (e.g., <i>ETV6</i> or <i>BCR</i>)		
Panel testing including <i>JAK2</i> , <i>CALR</i> , <i>MPL</i> , <i>CSF3R</i> , <i>ASXL1</i> , <i>TET2</i> , <i>EZH2</i> , <i>IDH1/2</i> , <i>DNMT3A</i> , <i>TP53</i> , <i>SF3B1</i> , <i>SRSF2</i> , <i>U2AF1</i> , <i>CBL</i> , <i>N/KRAS</i> , <i>SETBP1</i> , others	For a more complete list of recommended panel options, see numerous other papers, reviewed in McClure <i>et al.</i> Journal of Molecular Diagnostics, pending publication	Clonality may be used to support a diagnosis of an MPN in the correct clinical/pathologic context (e.g., triple negative MPNs, CEL vs HES) Specific patterns may suggest other entities <i>SF3B1</i> mutations may suggest MDS-RS or MDS/MPN-RS-T <i>CBL</i> mutations may suggest CMML	Provides diagnostic information to support single gene testing Adds additional prognostic information (e.g., <i>ASXL1</i> or <i>TP53</i> mutations or high number of mutations portend poor prognosis) May suggest pending progression (e.g., <i>NRAS</i> mutations, elevated <i>JAK2</i> VAF)

Where to Test: Testing should be performed in the laboratories that are certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity (molecular pathology) testing.

References: NCCN Guidelines for Chronic Myeloid Leukemia (v1.2018) and Myeloproliferative Neoplasms (v2.2018)

