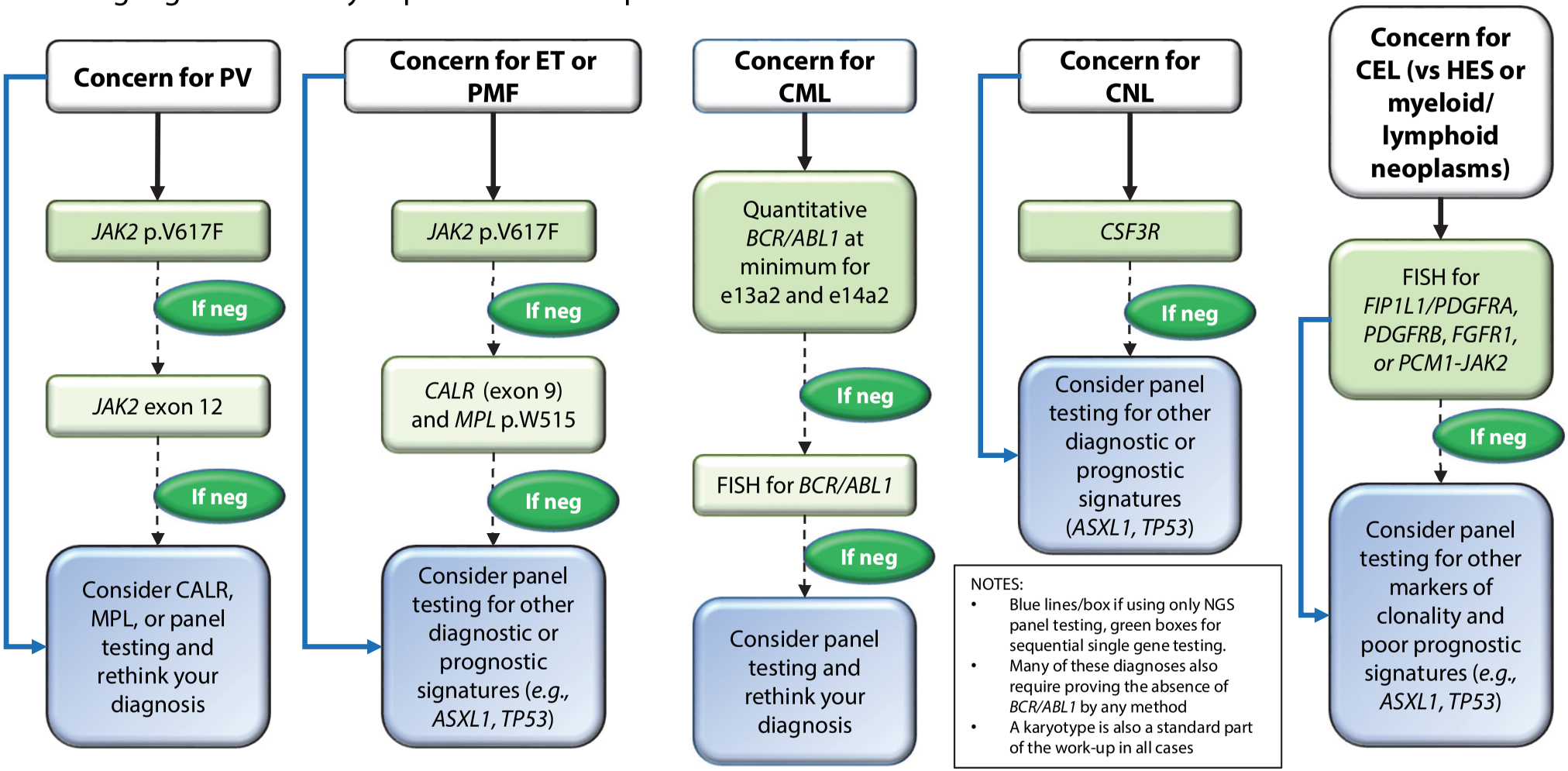
Molecular In My Pocket™

ONCOLOGY: *Myeloproliferative Neoplasms*

Testing Algorithm for Myeloproliferative Neoplasms



NOTES:

- Blue lines/box if using only NGS panel testing, green boxes for sequential single gene testing.
- Many of these diagnoses also require proving the absence of *BCR/ABL1* by any method
- A karyotype is also a standard part of the work-up in all cases

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

Prepared by the Association for Molecular Pathology Training and Education Committee
For more educational resources, see: *www.amp.org/education/education-overview/*

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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
BCR/ABL1	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 BCR/ABL1 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
JAK2	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
CALR	Exon 9 frameshift mutations	Diagnosis: CALR 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
MPL	p.W515K/L activating hotspot	Diagnosis: MPL 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
CSF3R	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
FIP1L1/PDGFRA	Usually cryptic deletion involving CHIC2	Diagnosis: identify specific subtype of neoplasms Therapy response: PDGFRA/B fusions are typically responsive to kinase inhibitors such as imatinib FGFR1 fusions are typically non-responsive to imatinib and may need newer agents	Fusions involving PDGFRA/B, FGFR1, and JAK2 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
PDGFRB/various partners	Various fusion partners, most commonly ETV6		
FGFR1/various partners	Various fusion partners		
PCM1-JAK2	Also includes other partners of JAK2 (e.g., ETV6 or BCR)		
Panel testing including *JAK2, CALR, MPL, CSF3R, ASXL1, TET2, EZH2, IDH1/2, DNMT3A, TP53, SF3B1, SRSF2, U2AF1, CBL, N/KRAS, SETBP1*, others	For a more complete list of recommended panel options, see numerous other papers, reviewed in McClure et al. 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 SF3B1 mutations may suggest MDS-RS or MDS/MPN-RS-T CBL mutations may suggest CMML	Provides diagnostic information to support single gene testing Adds additional prognostic information (e.g., ASXL1 or TP53 mutations or high number of mutations portend poor prognosis) May suggest pending progression (e.g., NRAS mutations, elevated JAK2 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)