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| CLINICAL Utility of Molecular Testing in  CLassical Myeloproliferative Neoplasms  Diagnostic UTILITY  Classical *BCR*::*ABL1*-negative myeloproliferative neoplasms (MPN) include polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). The presence of mutations in *JAK2* (>95% PV and 50%-60% of ET/PMF), *CALR* (25%-30% ET/PMF) or *MPL* (~5% ET/PMF) constitutes a major diagnostic criterion in these neoplasms.  *JAK2* exon 12 mutations are seen in Val617Phe negative PV and are associated with isolated erythrocytosis. They may also be rarely observed in myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)1.  Approximately 10% of ET/PMF lack the typical driver mutations in *JAK2*/*CALR*/*MPL* (‘triple-negative MPN’); the diagnosis can be supported by the presence of an alternative clonal marker (*e.g.* *ASXL1*, *EZH2*, *TET2*, *IDH1*, *IDH2*, *SRSF2*) in the appropriate clinicopathological context.  Co-mutation of *JAK2*/*CALR*/*MPL* is a rare but recognised phenomenon, most frequently occurring in cases with a low *JAK2* allele burden (<5%)2. *BCR*::*ABL1* may also rarely co-occur.  Acquired uniparental disomy / copy-neutral loss of heterozygosity of 9p24 is observed in approximately 30%-50% of PV and 20% of PMF, often manifesting as a high *JAK2* Val617Phe allele burden. This is rarely seen in ET, therefore a high *JAK2* Val617Phe should prompt consideration of a diagnosis PV, PMF or post-ET/PV MF3,4.  *JAK2* Val617Phe mutations can also occur in chronic myelomonocytic leukaemia (CMML) and are typically associated with proliferative features5. *MPL*, *CALR* and *CSF3R* mutations are rarely observed in CMML.  The diagnosis of MDS/MPN-RS-T is strongly supported by the presence of an *SF3B1* mutation together with a *JAK2* (most common), *CALR* or *MPL* mutation6.  Mutations in *ASXL1*, spliceosome genes, and RAS pathway genes are uncommon in chronic phase MPN (ET and PV), therefore a diagnosis of PMF, post-ET MF and post-PV MF should be considered4,7.  The presence of mutations in *IDH1*/*IDH2* or *TP53* in addition to *JAK2*/*CALR*/*MPL* should raise suspicion of transformation to blast-phase MPN4,8.  Somatic mutations in *SH2B3* are observed in 5%-7% of MPNs and may co-occur with another typical MPN driver mutation (*JAK2*/*CALR*/*MPL*), as well as being also observed in idiopathic erythrocytosis9.  Prognostic Utility  ‘Triple-negative’ PMF has been associated with inferior leukaemia-free and overall survival (noting that there is no standard definition of this entity)10.  In PMF (MIPSS70+v2.0), absence of type 1/type-1 like *CALR* and presence of high molecular risk mutations (*ASXL1*, *SRSF2*, *U2AF1* Gln157, *EZH2* and *IDH1*/*IDH2*) are considered adverse risk features11. *NRAS*/*KRAS* mutations have also been associated with inferior survival in both primary and secondary myelofibrosis12,13.  Integrated clinical-molecular prognostic scoring systems for MPNs that incorporate high risk molecular features include: MIPSS-PV (*SRSF2*)14, MIPSS-ET (*SF3B1*, *SRSF2*, *U2AF1* and *TP53*)14, MYSEC-PM for post-PV/ET MF (*CALR*-unmutated)15, Myelofibrosis Transplant Scoring System (MTSS) for both primary and post-PV/ET MF (non-*CALR*/*MPL* driver mutation and *ASXL1* mutation)16, and the MPN personalised risk model4.  Biomarkers of response to therapy  Ruxolitinib and other JAK inhibitors may be effective in PMF and post-PV/ET MF regardless of *JAK2* mutation status17.  Treatment with interferon alpha in patients with MPN may induce a reduction in mutant allele burden (including complete molecular remission) in a subset of patients18.  References  **1.** Scott LM. The JAK2 exon 12 mutations: a comprehensive review. *Am J Hematol* 2011; **86**(8): 668-76. **2.** Mora B, et al. Platelet count predicts driver mutations' co-occurrence in low JAK2 mutated essential thrombocythemia and myelofibrosis. *Leukemia* 2021; **35**(5): 1490-3. **3.** Wang L, et al. Acquired uniparental disomy of chromosome 9p in hematologic malignancies. *Exp Hematol* 2016; **44**(8): 644-52. **4.** Grinfeld J, et al. Classification and Personalized Prognosis in Myeloproliferative Neoplasms. *N Engl J Med* 2018; **379**(15): 1416-30. **5.** Pich A, et al. JAK2V617F activating mutation is associated with the myeloproliferative type of chronic myelomonocytic leukaemia. *J Clin Pathol* 2009; **62**(9): 798-801. **6.** WHO Classification of Tumours Editorial Board. 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