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| Clinical Utility of Molecular Testing in myelodysplastic/myeloproliferative neoplasms  Diagnostic utility  To establish a diagnosis of a myelodysplastic/myeloproliferative neoplasm (MDS/MPN), molecularly defined neoplasms that present with similar or overlapping features must be ruled out including *BCR-ABL1*-positive CML and myeloid neoplasms with rearranged *PDGFRA*, *PDGFRB*, *FGFR1,* and *PCM1-JAK2*.  Gene mutations are seen in >90% of patients with chronic myelomonocytic leukaemia (CMML) and the presence of a clonal marker comprises a WHO diagnostic criterion1. While there is no mutation specific for CMML, the combination of *SRSF2* and *TET2* mutations is particularly suggestive of CMML2. Additional genes mutated in CMML include *ASXL1* (40%), RAS pathway genes *e.g.* *NRAS*, *KRAS*, *CBL* (30%), *SETBP1* (15%) and *RUNX1* (15%)3.  In a patient with suspected CMML, the absence of mutations detected by this panel should prompt reconsideration of the diagnosis of CMML.  *JAK2* Val617Phe mutations can occur in CMML and are associated with proliferative features4. *MPL*, *CALR* and *CSF3R* mutations are rare in CMML and their presence should prompt consideration of alternative diagnoses such as a myeloproliferative neoplasm (MPN).  Atypical chronic myeloid leukaemia, *BCR-ABL1*-negative (aCML) and CMML have overlapping genomic profiles. aCML is enriched for mutations in *SETBP1*, *ASXL1*, *EZH2* and *ETNK1*2,5.  The finding of a *CSF3R* Thr618Ile or other activating *CSF3R* mutation constitutes a major WHO diagnostic criterion for chronic neutrophilic leukaemia (CNL), although it is not required for diagnosis if other criteria are fulfilled1. The absence of a *CSF3R* mutation however should prompt careful review of the diagnosis. *CSF3R* mutations are reported at variable frequencies in aCML and other MDS/MPNs6,7.  Concurrent genes mutated in CNL with *CSF3R* mutations include but are not limited to *ASXL1*, *SETBP1*, *SRSF2* and *TET28.*  The diagnosis of myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) is strongly supported by the presence of an *SF3B1* mutation together with a *JAK2* (most common), *CALR* or *MPL* mutation1.  The molecular profile of myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U) is heterogeneous and there is frequent overlap with other MDS/MPNs. In the appropriate clinicopathological context, the finding of mutations in *ASXL1*, *SRSF2*, *SETBP1*, *JAK2*, *NRAS*, *RUNX1* and/or *TET2* would support the diagnosis of MDS/MPN-U2,3.  The finding of an activating point mutations at codon 816 of *KIT* (most commonly *KIT* Asp816Val) should prompt consideration of an associated mast cell neoplasm.  Somatic mutations detected in MDS/MPNs typically persist upon transformation to AML.  *NPM1* and *FLT3* mutations are very uncommon in MDS/MPNs and if present suggest a diagnosis of AML in evolution.  Prognostic utility  Mutations in *ASXL1*, *RUNX1*, *NRAS* and *SETBP1* are associated with inferior overall survival in CMML and are incorporated into the CPSS-Mol score9.  *SETBP1* mutations have been associated with a higher leukocyte count and inferior outcomes in aCML10.  References  **1.** Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **2.** Palomo L, et al. Molecular landscape and clonal architecture of adult myelodysplastic/myeloproliferative neoplasms. *Blood* 2020; **136**(16): 1851-62. **3.** Patnaik MM, Lasho TL. Genomics of myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes. *Hematology Am Soc Hematol Educ Program* 2020; **2020**(1): 450-9. **4.** 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. **5.** Gambacorti-Passerini CB, et al. Recurrent ETNK1 mutations in atypical chronic myeloid leukemia. *Blood* 2015; **125**(3): 499-503. **6.** Maxson JE, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. *N Engl J Med* 2013; **368**(19): 1781-90. **7.** Zhang H, et al. Genomic landscape of neutrophilic leukemias of ambiguous diagnosis. *Blood* 2019; **134**(11): 867-79. **8.** Szuber N, et al. Chronic neutrophilic leukemia: 2020 update on diagnosis, molecular genetics, prognosis, and management. *Am J Hematol* 2020; **95**(2): 212-24. **9.** Elena C, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. *Blood* 2016. **10.** Piazza R, et al. Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. *Nat Genet* 2013; **45**(1): 18-24. |