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| Clinical Utility of Molecular Testing in MYELODYSPLASTIC NEOPLASMS (MDS)  DiagnosTiC Utility  The most commonly mutated genes in MDS include genes involved in RNA splicing (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*), DNA methylation (*DNMT3A*, *TET2*, *IDH1*, *IDH2*), chromatin and histone modification (*ASXL1*, *EZH2*), signal transduction (*NRAS*, *KRAS*, *CBL*), transcription (*RUNX1*, *GATA2*) and tumour suppressor genes (*TP53*)1-4.  The majority of patients with MDS (80%-90%) will have one of the common myeloid mutations, and therefore cases without molecular or cytogenetic abnormalities should prompt consideration of non-MDS causes of cytopenias5.  WHO 5th edition has defined three categories of MDS with defining genetic abnormalities: MDS-5q (in isolation or with one other cytogenetic abnormality other than -7/del7q); MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*); and MDS with biallelic TP53 inactivation (MDS-bi*TP53*)6.  MDS-*SF3B1* is defined by the presence of an *SF3B1* mutation (VAF ≥5%) and absence of del(5q), monosomy 7, or complex karyotype, *regardless* of the percentage of ring sideroblasts (previous threshold was 5%). MDS cases with wild-type *SF3B1* and ≥15% ring sideroblasts are now classified as MDS with low blasts and ring sideroblasts (MDS-LB-RS)6,7.  Evidence of multihit *TP53* alteration includes >1 *TP53* mutation, *TP53* mutation and 17p loss on cytogenetics/FISH, or a *TP53* mutation with a high VAF. However, multihit *TP53* alteration may be present without these features and is technically difficult to detect by NGS panel testing alone.  Somatic mutations detected in MDS typically persist upon transformation to AML. Transformation is also associated with acquisition of additional mutations8.  The presence of mutations in *JAK2*, *CALR*, *MPL*, *CSF3R* and/or *SETBP1* should raise suspicion of an underlying myeloproliferative neoplasm or a myelodysplastic/myeloproliferative neoplasm.  The detection of a *STAT3* or *STAT5B* mutation in a patient with MDS suggests the presence of a co-existing large granular lymphocyte (LGL) clone9. The prevalence of LGL clones in MDS is highly variable across studies (range 1.4% to 49%)10.  MDS may occur as part of VEXAS syndrome which is characterised by somatic (acquired) mutations in *UBA1*11. Comutations in genes associated with myeloid neoplasms have also been observed in some cases12,13.  *UBTF* tandem duplications (*UBTF*-TD) have been recently described as a distinct entity in AML14,15, but could also be observed in MDS, particularly in higher risk MDS16,17.  Mutations in *RUNX1*, *GATA2*, *DDX41* and *ETV6* shouldraise the suspicion of a germline predisposition to myeloid neoplasm.  Prognostic Utility  The IPSS-M, incorporating somatic gene mutations, has improved prognostic accuracy compared to the IPSS-R (https://mds-risk-model.com)4. *TP53*multihit,mutations in *FLT3* (both ITD and TKD)and *KMT2A (MLL)* partial tandem duplication (PTD) have been ranked as the strongest predictors of adverse outcome in IPSS-M, followed by mutations in *ASXL1*, *CBL*, *DNMT3A*, *ETV6*, *EZH2*, *IDH2*, *KRAS*, *NPM1*, *NRAS*, *RUNX1*, *SRSF2*, and *U2AF1*4,18.  Inferior outcomes in MDS are consistently associated with a higher number of driver mutations4.  S*F3B1* mutations in isolation are associated with favourable outcomes in MDS when not co-occurring with poor risk features. Co-mutations with *DNMT3A*, *TET2*,and/or *ASXL1* only do not appear to abrogate the favourable prognostic impact of *SF3B1* mutation3,4.  *TP53* mutations in MDS with del(5q) are associated with early clonal evolution, disease progression and poorer prognosis19.  Biomarkers of response to therapy  *IDH1* and *IDH2* mutations are observed in approximately 5% of MDS and represent a potential target of IDH1 andIDH2 inhibitor class of therapeutics, respectively20,21.  MDS/AML with *UBTF*-TD has a transcriptional signature similar to *KMT2A*-rearranged AML, including *HOX* gene dysregulation, and is potentially targetable by menin inhibitors21,22.  REFERENCES  **1.** Haferlach T, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia* 2014; **28**(2): 241-7. **2.** Papaemmanuil E, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* 2013; **122**(22): 3616-27; quiz 99. **3.** Bersanelli M, et al. Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes. *J Clin Oncol* 2021; **39**(11): 1223-33. **4.** Bernard E, et al. 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