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| Clinical Utility of Molecular Testing in MYELODYSPLASTIC SYNDROME  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 cytopenias4-6.  Mutations in *SF3B1* are strongly associated with the presence of ring sideroblasts. The finding of an *SF3B1* mutation reduces the percentage of ring sideroblasts required to confirm a diagnosis of MDS with ring sideroblasts (MDS-RS) from ≥15% to ≥5%1,7,8.  Evidence of multihit *TP53* alteration includes >1 *TP53* mutation, *TP53* mutation + 17p loss on cytogenetics/FISH or a *TP53* mutation with a high variant allele frequency. However, multihit *TP53* alteration may be present without these features and is technically difficult to detect by NGS panel testing alone. MDS with biallelic *TP53* inactivation (MDS-bi*TP53*) is included as a new category in the WHO 5th edition8.  Somatic mutations detected in MDS typically persist upon transformation to AML. Transformation is also associated with acquisition of additional mutations9.  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) clone10,11. The prevalence of LGL clones in MDS is highly variable across studies (range 1.4% to 49%)12.  *NPM1* mutations are rarely observed in myelodysplastic syndrome (MDS) and myelodysplastic/myeloproliferative neoplasms. Patients with a blast count <20% and an *NPM1* mutation typically show rapid transformation to AML. These cases are biologically and clinically more similar to AML in evolution4,13,14.  Mutations in *RUNX1*, *GATA2*, *DDX41* and *ETV6* shouldraise the suspicion of a germline predisposition to myeloid neoplasm.  MDS may occur as part of VEXAS syndrome which is characterised by somatic (acquired) mutations in *UBA1* (not currently targeted by this assay)15,16. Concomittant mutations in genes associated with myeloid neoplasms have also been observed in some cases17,18.  Prognostic Utility  The IPSS-M, incorporating somatic gene mutations, has improved prognostic accuracy compared to the IPSS-R (https://mds-risk-model.com)6.  Inferior outcomes in MDS are consistently associated with a higher number of driver mutations3,6.  *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 MDS6. Additionally, mutations in *ASXL1*, *BCOR*, *EZH2*, *NRAS*, *RUNX1*, *STAG2*, and *U2AF1* are associated with inferior leukaemia-free survival (LFS), overall survival (OS), and AML transformation6,19,20.  S*F3B1* mutations are associated with favourable outcomes in MDS when not co-occurring with poor risk features2,4,6.  MDS with splicing gene mutations other than *SF3B1* have been associated with inferior outcomes4.  *TP53* mutations in MDS with del(5q) are associated with early clonal evolution, disease progression and poorer prognosis21.  Biomarkers of response to therapy  *IDH1* and *IDH2* mutations are observed in approximately 5% of MDS22,23 and represent a potential target of *IDH1* and *IDH2* inhibitor class of therapeutics, respectively.  References  **1.** Swerdlow S, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **2.** Haferlach T, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia* 2014; **28**(2): 241-7. **3.** Papaemmanuil E, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* 2013; **122**(22): 3616-27. **4.** 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. **5.** Steensma DP, et al. 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