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| cLINICAL UTILITY OF MOLECULAR TESTING IN  Acquired Aplastic Anaemia AND HYpoplastic mds  Diagnostic Utility  Distinguishing between hypoplastic myelodysplastic syndrome (h-MDS) and aplastic anaemia (AA) may be challenging on both morphological and molecular assessments. h-MDS has been observed to have more mutations per patient and higher mean VAF than AA1. However compared to typical MDS, h-MDS has fewer mutations per patient and a lower frequency of mutations in *SF3B1*, *SRSF2, ASXL1* and *TET2*1.  Clonal haematopoiesis is detectable in a significant proportion of patients with aplastic anaemia (AA) both at time of diagnosis and following immunosuppressive therapy2,3.  Somatic mutations observed in AA include those commonly observed in MDS such as *ASXL1* and *DNMT3A*, as well as those more specific to AA such as *PIGA* (associated with a PNH clone), *BCOR* and *BCORL13*.  Copy number-neutral loss of heterozygosity of chromosome 6p is relatively specific to AA, occurring in ~12% of AA but <1% of MDS4-6. This is not assessed by this assay.  A subset of patients with AA and h-MDS may have *STAT3* mutations detectable indicating the presence of subclinical T-cell clones7.  The presence of hypoplastic MDS (particularly in paediatric patients) should prompt consideration of underlying inherited pathogenic mutations in genes such as *GATA2*, *SAMD9* and *SAMD9L*.  Prognostic Utility  Mutations in *PIGA*, *BCOR* and *BCORL1* have been associated with a better response to immunosuppressive therapy and improved progression-free and overall survival3.  MDS-associated somatic mutations (*e.g.* *ASXL1*, *DNMT3A*, *RUNX1)* have been associated with an increased risk of progression to secondary MDS3,8,9.  References  **1.** Bono E, et al. Clinical, histopathological and molecular characterization of hypoplastic myelodysplastic syndrome. *Leukemia* 2019. **2.** Babushok DV, et al. Emergence of clonal hematopoiesis in the majority of patients with acquired aplastic anemia. *Cancer Genet* 2015; **208**(4): 115-28. **3.** Yoshizato T, et al. Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia. *N Engl J Med* 2015; **373**(1): 35-47. **4.** Betensky M, et al. Clonal evolution and clinical significance of copy number neutral loss of heterozygosity of chromosome arm 6p in acquired aplastic anemia. *Cancer Genet* 2016; **209**(1-2): 1-10. **5.** Katagiri T, et al. Frequent loss of HLA alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia. *Blood* 2011; **118**(25): 6601-9. **6.** Score J, et al. Detection of leukemia-associated mutations in peripheral blood DNA of hematologically normal elderly individuals. *Leukemia* 2015; **29**(7): 1600-2. **7.** Jerez A, et al. STAT3 mutations indicate the presence of subclinical T-cell clones in a subset of aplastic anemia and myelodysplastic syndrome patients. *Blood* 2013; **122**(14): 2453-9. **8.** Negoro E, et al. Origins of myelodysplastic syndromes after aplastic anemia. *Blood* 2017; **130**(17): 1953-7. **9.** Kulasekararaj AG, et al. Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome. *Blood* 2014; **124**(17): 2698-704. |