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| Clinical Utility of Molecular Testing in THE INVESTIGATION OF CYTOPENIAS  DiagnosTIC Utility   * The detection of assumed somatic mutations in patients undergoing investigations for cytopenias defines the presence of a clonal haematological process which may be classified (depending on clinicopathological features) as clonal cytopenias of uncertain significance (CCUS) or an overt myeloid neoplasm such as myelodysplastic syndrome (MDS). * The spectrum of genes that are mutated in CCUS and MDS is similar and include genes such as *DNMT3A*, *TET2*, *ASXL1* (collectively termed ‘DTA’ mutations), *SF3B1*, *SRSF2* and *U2AF1*. * The majority of patients with MDS (~80%) will have one of the common myeloid mutations, and therefore cases without molecular or cytogenetic abnormalities should prompt consideration of non-MDS causes of cytopenias1,2. Other acquired abnormalities may be present in CCUS and MDS that are not detectable by this assay such as copy number changes and testing for these should also be considered depending on clinical context. * *PIGA* mutations may be observed in paroxysmal nocturnal haemoglobinuria (PNH), aplastic anaemia and MDS3,4. The finding of a *PIGA* mutation should prompt consideration of these diagnoses and testing for the presence of a PNH clone. * Approximately 90% of patients investigated for chronic isolated neutropenia have no evidence of clonal haematopoiesis. These patients are at low risk for subsequent development of a myeloid neoplasm5.   The finding of an activating *STAT3* or *STAT5B* mutation supports a diagnosis of T-cell large granular lymphocytic leukaemia (T-LGL) or chronic lymphoproliferative disorder of NK cells (CLPD-NKs) in the appropriate clinicopathological context6-8. However approximately 50% of T-LGL and CLPD-NKs cases do not have a detectable *STAT3* or *STAT5B* mutation.  VEXAS (vacuoles, E1 enzyme, X chromosome, autoinflammatory, somatic) syndrome is characterised by somatic (acquired) mutations in *UBA1*9,10 (not currently targeted by this assay)*.* Associated haematologic abnormalities include cytopenias, myeloid neoplasms and charateristic cytoplasmic vacuoles in granulocytic and erythroid precursors9,10. Concomittant mutations in genes associated with clonal haematopoiesis and myeloid neoplasms have also been observed in some cases11,12.  Prognostic Utility  Clonal haematopoiesis is associated with an increased risk of subsequent diagnosis of haematological malignancy, however most individuals who acquire clonal haematopoiesis during aging will never develop haematologic disease, with the risk estimated at 0.5%-1% per year13,14.  In clonal haematopoiesis, factors associated with a risk of progression to a myeloid neoplasm include (i) the types of mutations (*e.g.*, *TP53*,spliceosome genes, *IDH1*, *IDH2*, and co-mutation with DTA) (ii) the number of mutations (≥2) (iii) a higher variant allele frequency (VAF ≥10%), and (iv) abnormal blood cell indices15-18.  Patients with “high-risk” CCUS as described above have a similar overall survival to that observed in patients with a diagnosis of MDS with a similar mutation pattern17.  Evolution of CCUS to a myeloid neoplasm is often associated with acquisition of new mutations and/or clonal expansion (increase in variant allele frequency)18.  In patients with CCUS, *SF3B1* mutations are almost invariably associated with subsequent development of overt MDS with ring sideroblasts19.  References  **1.** Steensma DP, et al. 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