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| cLINICAL UTILITY OF MOLECULAR TESTING IN  Clonal Haematopoiesis  Diagnostic Utility  The detection of assumed somatic mutations in the peripheral blood or bone marrow is consistent with the presence of clonal haematopoiesis.  In the absence of fulfilling diagnostic criteria for a hematologic malignancy, this may be termed clonal haematopoiesis of indeterminate potential (CHIP) or age-related clonal haematopoiesis (ARCH) if the peripheral counts are normal, and clonal cytopenias of undetermined significance (CCUS) when there are cytopenias1.  There is significant clinical and molecular overlap between CCUS and lower-risk MDS2.  The most commonly mutated genes in clonal haematopoiesis are *DNMT3A*, *TET2* and *ASXL1* (DTA)3,4, however many other genes mutated in myeloid neoplasms are also observed in clonal haematopoiesis and CCUS including, but not limited to, *JAK2*, *TP53*, *PPM1D*,spliceosome genes (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2)*, *IDH1*, *IDH2*, *EZH2*, *RUNX1* and *CBL*3-6.  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 year3,4.  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 indices5-8.  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 pattern5.  Evolution of CCUS to a myeloid neoplasm is associated with either acquisition of new mutations or clonal expansion (increase in variant allele frequency)6.In patients with CCUS, *SF3B1* mutations are almost invariably associated with subsequent development of overt MDS with ring sideroblasts9.  Clonal haematopoiesis risk score (CHRS) was developed to assess the risk of myeloid neoplasm in patients with CHIP/CCUS. Variables included single *DNMT3A* mutations (favourable), high-risk mutations (*SRSF2*, *SF3B1*, *ZRSR2*, *IDH1*, *IDH2*, *FLT3*, *RUNX1*, *JAK2* and *TP53*), ≥2 mutations, VAF ≥20%, age ≥65 years, presence of cytopenias, and red cell indices. Note *TP53* did not significantly alter the performance of this model but was empirically included, and *U2AF1* was not included in the analysis10,11.  References  **1.** Steensma DP, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* 2015; **126**(1): 9-16. **2.** Li M, et al. Clinical, molecular, and prognostic comparisons between CCUS and lower-risk MDS: a study of 187 molecularly annotated patients. *Blood Advances* 2021; **5**(8): 2272-8. **3.** Jaiswal S, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014; **371**(26): 2488-98. **4.** Genovese G, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med* 2014; **371**(26): 2477-87. **5.** Malcovati L, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. *Blood* 2017; **129**(25): 3371-8. **6.** Gallì A, et al. Relationship between clone metrics and clinical outcome in clonal cytopenia. *Blood* 2021; **138**(11): 965-76. **7.** Warren JT, Link DC. Clonal hematopoiesis and risk for hematologic malignancy. *Blood* 2020; **136**(14): 1599-605. **8.** Desai P, et al. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat Med* 2018; **24**(7): 1015-23. **9.** Malcovati L, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. *Blood* 2020; **136**(2): 157-70. **10.** Weeks LD, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. *NEJM Evid* 2023; **2**(5). **11.** Weeks LD, et al. Prediction of Risk for Myeloid Malignancy in Clonal Hematopoiesis. *NEJM Evidence* 2023; **2**(5): EVIDoa2200310. |