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| Clinical utility of molecular testing in  acute myeloid leukaemia  Diagnostic Utility  In the WHO 5th edition classification, acute myeloid leukaemia (AML) with defining genetic abnormalities include acute promyelocytic leukaemia (APL) with *PML*::*RARA* fusion, AML with specific gene fusions (*RUNX1*::*RUNX1T1*, *CBFB*::*MYH11*, *DEK*::*NUP214*, *RBM15*::*MRTFA* and *BCR*::*ABL1* fusion), gene rearrangements (*KMT2A*, *MECOM* and *NUP98*), and gene mutations (*NPM1, CEBPA* and myelodysplasia-related [MR]). A diagnosis of AML can be made regardless of blast count in the presence of these defining genetic abnormalities, with the exception of AML with *BCR*::*ABL1* fusion, AML with *CEBPA* mutation and AML-MR (which require at least 20% blasts)1*.*  Defining somatic mutations for AML-MR include *ASXL1*, *BCOR, EZH2*, *SF3B1*, *SRSF2*, *STAG2, U2AF1* and *ZRSR2*. Note *RUNX1* is also included by the International Consensus Classification (ICC)2.  Emerging or provisional AML subtypes in the WHO 5th edition classification and/or the ICC include AML with *CBFA2T3*::*GLIS2*, *KAT6A*::*CREBBP*, *FUS*::*ERG*, *MNX*::*ETV6*, *NPM1*::*MLF1*, *PRDM16*::*RPN1*, *PICALM*::*MLLT10*, and *RUNX1*::*CBFA2T3*.  AML with *BCR*::*ABL1* fusion is a rare *de novo* AML, or alternatively represents blast phase of chronic myeloid leukaemia.  *KIT* mutations are rarely observed in non-core binding factor AML3; testing for t(8;21) and inv(16) should be considered.  *JAK2* Val617Phe mutations are infrequent in *de novo* AML; a preceding myeloproliferative neoplasm should be considered3.  AML with plasmacytoid dendritic cell expansion (pDC-AML) is characterised by pDC expansion and *RUNX1* mutations (70%)4.  The molecular profile of blastic plasmacytoid dendritic cell neoplasm (BPDCN) is not specific and resembles that of other myeloid neoplasms such as MDS and CMML, however *RUNX1* mutations are rarely observed5,6.  Acute erythroid leukaemia is characterised by a high prevalence of multi-hit *TP53* alterations and complex karyotype7.  UBTF tandem duplications (*UBTF*-TD) have been recently described as a recurrent lesion in paediatric and young adult AML, associated with morphologic dysplasia, normal karyotype or trisomy 8, and mutations in *WT1* and *FLT3*-ITD8,9.  In-frame insertion mutations in *CBFB* are similar to inv(16) AML but without the *CBFB*::*MYH11* fusion10.  Some mutations have potential germline predisposition: *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2* and *TP53*. Testing a remission and/or germline sample in the appropriate clinical context should be considered.  **Table. 2022 European LeukemiaNet (ELN) risk classification**  cid:image001.jpg@01D8BEB8.44339240Prognostic Utility  The ELN 2022 risk stratification incorporates baseline cytogenetic and molecular factors (Table)11.  MRD assessment is an independent prognostic indicator post therapy for AML, and may be a more potent predictor of outcome compared to the baseline clinical and molecular profile12,13.  *TP53* mutations and complex karyotype provide independent and additive prognostic information, with the combination having the worst outcome3.  BIOMARKERS OF RESPONSE TO THERAPY  *FLT3* mutations are the target of midostaurin14 (*FLT3*-ITD and TKD) (clinical trials included only TKD mutations at Asp835 and Ile836 codons), quizartinib (*FLT3*-ITD only)15 in newly diagnosed AML, and gilteritinib16 in relapsed/refractory AML.  *FLT3* testing should be repeated at relapse/progression as ~20% of patients have a change (gain or loss) in mutation status17.  *IDH1* (Arg132) and *IDH2* (both Arg140 and Arg172) mutations are the target of IDH1 and IDH2 inhibitors, respectively18.  APL with *PML*::*RARA* fusion is associated with excellent response to ATRA and arsenic trioxide treatment.  AML with *UBTF*-TD, *DEK*::*NUP214*, or *NUP98* rearrangement have a transcriptional signature similar to *KMT2A*-rearranged AML, including HOX gene dysregulation, and are potentially targetable by menin inhibitors19,20.  Acquired resistance to targeted inhibitors have been described with *FLT3* Phe691Leu (FLT3 inhibitors)21, second-site IDH1/IDH2 mutations (IDH1/IDH2 inhibitors)22, *BAX* (BCL2 inhibitors)23, and *MEN1* (menin inhibitors)24.  References  **1.** WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; forthcoming. 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