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| cLINICAL UTILITY OF MOLECULAR TESTING IN  Acute Leukaemias of MIXED OR Ambiguous Lineage  DIAGNOSTIC utility  Acute leukaemias of ambiguous lineage (ALAL) are a group of rare leukaemias encompassing acute undifferentiated leukaemia (AUL) and mixed phenotype acute leukaemia (MPAL)1.  The diagnosis of ALAL currently relies on immunophenotyping. The finding of recurrent gene rearrangements can help refine subclassification and also exclude other WHO-defined entities such as acute myeloid leukaemia (AML) with *RUNX1*::*RUNX1T1* and myeloid/lymphoid neoplasms with *FGFR1* rearrangement2.  In the WHO 5th edition, ALAL with defining genetic abnormalities include MPAL with *BCR*::*ABL1* fusion, MPAL with *KMT2A*-rearrangement, MPAL with *ZNF384* rearrangement and ALAL with *BCL11B* rearrangement1.  *BCR*::*ABL1* fusion occurs in 15%-20% of MPAL and is typically associated with a B/myeloid phenotype2.  MPAL with *KMT2A*-rearrangement is usually associated with a B/myeloid phenotype. Many different partner genes have been reported, with *AFF1*, *MLLT3* and *MLLT1* beingthe most common in MPAL.  *ZNF384* rearrangement occurs in approximately 50% of paediatric B/myeloid MPAL3. While the rearrangement is uncommon in adult MPAL, it may also be observed in both adult and paediatric B-lymphoblastic leukaemia (commonly in cases with aberrant myeloid antigen expression)3-5.  ALAL with *BCL11B* rearrangement can present as T/myeloid MPAL or AUL, or in some cases of early T-cell precursor (ETP) ALL.  Other recurrently reported gene rearrangements in MPAL include *PICALM*::*MLLT10* (T/myeloid) and *CBFA2T3*::*GLIS2* (T/megakaryocytic, occurs exclusively in paediatric patients).  While T/myeloid and B/myeloid MPAL have overlapping genomic profiles, *NOTCH1* mutations are not typically observed in B/myeloid MPAL5,6.  T/myeloid MPAL and ETP-ALL share a number of genomic features. Commonly mutated genes in T/myeloid MPAL include transcriptional regulators such as *WT1*, *ETV6*, *RUNX1* and *CEBPA*, signalling pathway genes (*FLT3*, *NRAS*, *KRAS*) and epigenetic modifiers (*DNMT3A*, *TET2*, *IDH1*, *IDH2* and inactivatibcng *EZH2* mutations)3,5,6.  Recurrently mutated genes in B/myeloid MPAL include transcriptional regulators (*RUNX1*, *WT1*, *PAX5*, *ETV6*), *FLT3* and RAS signalling genes (*NRAS*, *KRAS*, *PTPN11*)3,7. Copy number alterations affecting genes such as *IKZF1* may also be observed.  Recurrently reported alterations in AUL include *SET*::*NUP214* fusion and mutations in *PHF6*, *RUNX1*, *SRSF2*, *ASXL1* or *BCOR*.  *TP53* mutations have been observed in both T/myeloid and B/myeloid MPAL3,6.  *NPM1* mutations are specific to AML and have not been found in MPAL3,5.  BIOMARKERS OF RESPONSE TO THERAPY  Tyrosine kinase inhibitor therapy in combination with chemotherapy is recommended for MPAL with t(9;22)(q34.1;q11.2); *BCR*::*ABL1*8,9.  *FLT3* (TKD and ITD) and *IDH1* and *IDH2* mutations are the target of FLT3 and IDH inhibitors, respectively; however, data are limited in ALAL10,11.  The interaction between KMT2A fusion protein and its critical oncogenic cofactor, menin, can be targeted using small molecule inhibitors of menin, which have demonstrated potent pre-clinical efficacy12 and shown promising activity in early-phase clinical trials13.  REFERENCES  **1.** WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; forthcoming. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.fr. **2.** Swerdlow S, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). 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