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| CLINICAL Utility of Molecular Testing in  aml WITH MUTATED *NPM1*  Diagnostic Utility  *NPM1* mutations are the most common genetic abnormality in adult AML, accounting for approximately 30% of cases overall and a higher proportion in cases with a normal karyotype.  AML with mutated *NPM1* is a distinct entity in both the WHO 5th edition and International Consensus Classification (ICC)1,2.  While the diagnosis of AML with mutated *NPM1* can be made irrespective of the blast count according to the WHO 5th edition1, ≥10% blasts are required for the ICC2.  *DNMT3A, FLT3*-ITD*, TET2*, *IDH1* and *IDH2* (Arg140)mutations are enriched in AML with mutated *NPM1*3.  Prognostic Utility  AML with mutated *NPM1* is a heterogeneous group with significant gene-gene interactions.  Evaluation of *NPM1* and *FLT3*-ITD status represents a major pillar of the European LeukemiaNet (ELN) genetic-based risk stratification model for AML4. A favourable prognosis is observed with mutated *NPM1* without *FLT3*-ITD.The *FLT3*-ITD allelic ratio is no longer considered in the ELN 2022 risk classification; consequently, AML with mutated *NPM1* and a *FLT3*-ITD is now categorised in the intermediate-risk group, irrespective of the allelic ratio4.  While comutation of *NPM1*/*DNMT3A*/*FLT3*-ITD (triple mutant) has been associated with inferior outcomes in some studies3,5, this profile is considered intermediate risk according to ELN 2022 criteria4.  The presence of adverse-risk cytogenetic abnormalities in *NPM1*-mutated AML now defines adverse risk according to ELN 2022 criteria4,6.  A subset of AML with mutated *NPM1* cases have comutation with one or more of the myelodysplasia-related genes (*ASXL1*, *BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, or *ZRSR2*). For the time being, the ELN recommends that these should not be used as an adverse prognostic marker if they co-occur with *NPM14.*  Other examples of prognostication models that could be considered include the knowledge bank approach and the AML Classification and Risk Stratification Calculator7,8*.*  *NPM1* mutations are a suitable marker for measurable residual disease (MRD) monitoring9,10. Type A, B and D transcripts comprise approximately 90% of *NPM1* mutations.  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 profile9.  biomarkers of response to therapy  *FLT3*-ITD and *FLT3*-TKD mutations (clinical trials included only TKD mutations at Asp835 and Ile836 codons) are the target of midostaurin11 (in newly diagnosed AML) and gilteritinib12 (in relapsed/refractory AML).  Repeat *FLT3* testing at relapse or disease progression is recommended as approximately 20% of patients have a change (gain or loss) in *FLT3* mutation status13.  *IDH1* and *IDH2* mutations are the target of IDH1 and IDH2 inhibitors, respectively14.  Second-site *IDH1*/*IDH2* mutations have been described in patients with acquired resistance to IDH1/IDH2 inhibitors15.  References  **1.** Khoury JD, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* 2022. **2.** Arber DA, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. *Blood* 2022. **3.** Papaemmanuil E, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med* 2016; **374**(23): 2209-21. **4.** Döhner H, et al. 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