|  |  |  |
| --- | --- | --- |
| **Patient {{ patient\_info.Patient }}**  **URN** {{ patient\_info.URN }}  **DOB** {{ patient\_info.DOB }}  **Sex** {{ patient\_info.Sex }} | **Lab No** {{ patient\_info.Lab\_No }}  **Ext Ref** {{ patient\_info.Ext\_Ref }}  **Collected** {{ patient\_info.Collected }}  **Received** {{ patient\_info.Received }}  **Specimen** {{ patient\_info.Specimen }} | **Requester** {{ patient\_info.Requester }}  **Referral Lab** {{ patient\_info.Referral\_Lab }} |

**Clinical Indication** {{ other\_info.Clinical\_Indication }}

**Correlative Morphology** {{ other\_info.Correlative\_Morphology }}

**HAEMATOLOGICAL MALIGNANCY GENE PANEL REPORT**

**Test Description** {{ report\_title.Test\_Description}}

**Result Summary**

**{{ report\_title.Result\_Summary}}**

**fefef**

**fefefefe**

**Clinical Interpretation** {{ report\_title.Clinical\_Interpretation }}.

**Test Results**

**FLT3-ITD Analysis FLT3-ITD DETECTED BY SEPARATE ASSAY (see Reportable Variants table for details)**

**Reportable Variants** {{ report\_title. reportable\_variants\_description }}.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **ASSUMED ORIGIN** | **GENE** | **VARIANT** | **VRF**  **(%)** | **CLINICAL SIGNIFICANCE IN AML** |
| {%tr for gene in reportable\_variants %} |  |  |  |  |
| **{{ gene.ASSUMED\_ORIGIN }}** | **{{ gene.GENE }}** | **{{ gene.VARIANT }}** | **{{ gene.VRF }}** | **{{gene.CLINICAL\_SIGNIFICANCE\_IN\_AML }}** |
| **{%tr endfor %}** |  |  |  |  |

VRF – variant read frequency

**Test Methodology**

{{ Test\_Methodology }}

**Test Limitations**

{{ Test\_Limitations }}

**Panel Summary**

{{ Panel\_Summary.Summary }}

Gene coverage in this sample is as follows

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **Transcript** | **Targeted exons** | **Coverage at >500x**  **(%)** | **Gene** | **Transcript** | **Targeted exons** | **Coverage at >500x**  **(%)** | **Gene** | **Transcript** | **Targeted exons** | **Coverage at >500x**  **(%)** |
| ABL1 | NM\_005157.4 | 4-10 | 100 | FLT3\* | NM\_004119.2 | 14-15,17,20 | 100 | PHF6 | NM\_001015877.1 | 7-10 | 95 |
| ARAF | NM\_001654.4 | 7,10,15 | 100 | FYN | NM\_002037.5 | 7 | 100 | PIGA | NM\_002641.3 | All coding | 100 |
| ASXL1 | NM\_015338.5 | 10-12 | 100 | GATA1 | NM\_002049.3 | 2-6 | 100 | PLCG1 | NM\_002660.2 | 11 | 100 |
| BCL2 | NM\_000633.2 | All coding | 100 | GATA2 | NM\_032638.4 | All coding | 100 | PLCG2 | NM\_002661.3 | 16,19-20,24 | 100 |
| BIRC3 | NM\_001165.4 | 6-9 | 100 | ID3 | NM\_002167.4 | All coding | 100 | RHOA | NM\_001664.2 | 2 | 100 |
| BRAF | NM\_004333.4 | 15 | 100 | IDH1 | NM\_005896.2 | 4,7 | 100 | RUNX1 | NM\_001754.4 | All coding | 100 |
| BTK | NM\_000061.2 | 11,15-16 | 100 | IDH2 | NM\_002168.2 | 4,7 | 100 | SETBP1 | NM\_015559.2 | 4 | 100 |
| CALR | NM\_004343.3 | 9 | 100 | IRF8 | NM\_002163.2 | 3 | 100 | SF3B1 | NM\_012433.2 | 14-16 | 100 |
| CARD11 | NM\_032415.4 | 4-9,15,20 | 100 | JAK2 | NM\_004972.3 | 12-14,16 | 100 | SH2B3 | NM\_005475.2 | All coding | 98.6 |
| CBL | NM\_005188.3 | 8-9 | 100 | JAK3 | NM\_000215.3 | 11,13,15 | 94.9 | SRSF2 | NM\_003016.4 | 1 | 100 |
| CD274 | NM\_014143.3 | All coding,3'UTR | 100 | KIT | NM\_000222.2 | 8,10-11,17 | 100 | STAT3 | NM\_139276.2 | 6,13,15,18-21 | 100 |
| CD79B | NM\_000626.2 | 5,6 | 100 | KRAS | NM\_033360.2 | 2-4 | 100 | STAT5B | NM\_012448.3 | 16 | 100 |
| CEBPA | NM\_004364.3 | All coding | 100 | MAP2K1 | NM\_002755.3 | 2-3 | 100 | STAT6 | NM\_001178078.1 | 10,13,16 | 100 |
| CSF3R | NM\_156039.3 | 14,17 | 100 | MPL | NM\_005373.2 | 1-11 | 100 | TCF3 | NM\_001136139.2 | 17 | 100 |
| CXCR4 | NM\_003467.2 | 2^ | 100 | MYD88 | NM\_002468.4 | 4-5 | 100 | TET2 | NM\_001127208.2 | All coding | 100 |
| DDX41 | NM\_016222.2 | All coding | 100 | NOTCH1 | NM\_017617.3 | 26-28,34,3'UTR^ | 100 | TP53 | NM\_000546.5 | All coding | 100 |
| DNMT3A | NM\_022552.4 | All coding | 100 | NPM1 | NM\_002520.6 | 11 | 100 | U2AF1 | NM\_006758.2 | 2,6 | 100 |
| ETNK1 | NM\_018638.4 | 3 | 100 | NRAS | NM\_002524.4 | 2-4 | 97.4 | XPO1 | NM\_003400.3 | 15-16 | 100 |
| EZH2 | NM\_004456.4 | All coding | 100 | PDCD1LG2 | NM\_025239.3 | All coding,3'UTR | 100 | ZRSR2 | NM\_005089.3 | All coding | 100 |

\* Please note FLT3-ITDs are not detected with this assay. A separate assay may have been performed, result included in Test Results if sample tested. ^ Partial coverage of region

Please note variants may not be optimally detected in genes with less than 100% coverage. The gene coverage above is considered acceptable given the available information about the clinical context, however please contact the laboratory for further advice should specific genes covered at less than 100% require full coverage. A list of regions with suboptimal coverage is available upon request.

Please contact the laboratory on 03 8559 7284 if you wish to discuss this report further.

**Reported by {{** **Panel\_Summary.Reported­\_by }}**

**Authorised by {{** **Panel\_Summary.** **Authorized\_by }}**

**Reported {{** **Panel\_Summary.Reported }}**

**References**

1. {{ References }}

**CLINICAL UTILITY OF MOLECULAR TESTING IN ACUTE MYELOID LEUKAEMIA**

# DIAGNOSTIC UTILITY

* + In the WHO revised 4th edition classification, acute myeloid leukaemia (AML) with recurrent genetic abnormalities includes AML with mutated *NPM1*, AML with biallelic mutation of *CEBPA*, and AML with mutated *RUNX1* (provisional)*1.*
  + The presence of a mutation in *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR* or *STAG2* has been shown to be highly specific (>95%) for a diagnosis of secondary AML, even without a known antecedent MDS diagnosis3.
  + *KIT* mutations are rarely observed in non-core binding factor AML2 and therefore if detected, specific testing for t(8;21) and inv(16) should be considered.
  + *JAK2* Val617Phe mutations are infrequent in *de novo* AML (approximately 1%) and therefore a preceding myeloproliferative neoplasm should be considered if detected2.
  + AML with plasmacytoid dendritic cell expansion (pDC-AML) is a recently described entity representing a subset of AML with pDC expansion and high frequency of *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.
  + 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.

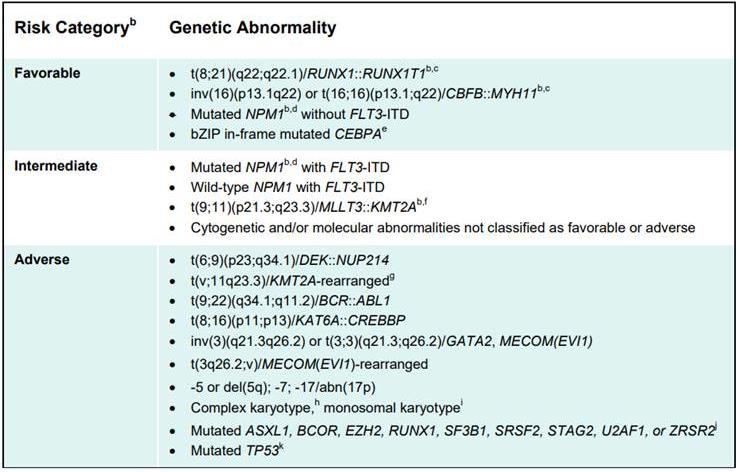
# PROGNOSTIC UTILITY

* + The ELN 2022 risk stratification incorporates baseline cytogenetic and molecular factors (Table)7. Major changes include *CEBPA* in-frame mutations in the bZIP domain, secondary AML-like gene mutations, and removal of the allelic ratio threshold for *FLT3*- ITD.
  + Other examples of prognostication models include the knowledge bank approach and the AML Classification and Risk Stratification Calculator8,9.
  + 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 profile10,11.
  + *TP53* mutations and complex karyotype provide independent and additive prognostic information, with the combination having the worst outcome2.

# BIOMARKERS OF RESPONSE TO THERAPY

**Table. 2022 European LeukemiaNet (ELN) risk classification**

* + *FLT3*-ITD and *FLT3*-TKD mutations (clinical trials included only TKD mutations at Asp835 and Ile836 codons) are the target of midostaurin12 (in newly diagnosed AML) and gilteritinib13 (in relapsed/refractory AML).



* + Repeat *FLT3* testing at relapse or disease progression is recommended as ~20% of patients have a change (gain or loss) in *FLT3*

mutation status14.

* + *IDH1* (Arg132) and *IDH2* (both Arg140 and Arg172) mutations are the target of IDH1 and IDH2 inhibitors, respectively15.
  + Second-site *IDH1*/*IDH2* mutations have been described in patients with acquired resistance to IDH1/IDH2 inhibitors16.

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**1.** Swerdlow S, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **2.** Papaemmanuil E, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med* 2016; **374**(23): 2209-21. **3.** Lindsley RC, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood* 2015; **125**(9): 1367-76. **4.** Xiao W, et al. Plasmacytoid dendritic cell expansion defines a distinct subset of RUNX1-mutated acute myeloid leukemia. *Blood* 2021; **137**(10): 1377-91. **5.** Stenzinger A, et al. Targeted ultra-deep sequencing reveals recurrent and mutually exclusive mutations of cancer genes in blastic plasmacytoid dendritic cell neoplasm. *Oncotarget* 2014; **5**(15): 6404-13. **6.** Menezes J, et al. Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm. *Leukemia* 2014; **28**(4): 823-9. **7.** Döhner H, et al. Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood* 2022. **8.** Gerstung M, et al. Precision oncology for acute myeloid leukemia using a knowledge bank approach. *Nat Genet* 2017; **49**(3): 332-40. **9.** Tazi Y, et al. Unified classification and risk-stratification in Acute Myeloid Leukemia. *Nature Communications* 2022; **13**(1): 4622. **10.** Jourdan E, et al. Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. *Blood* 2013; **121**(12): 2213-23. **11.** Ivey A, et al. Assessment of Minimal Residual Disease in Standard-Risk AML. *N Engl J Med* 2016; **374**(5): 422-33. **12.** Stone RM, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *N Engl J Med* 2017; **377**(5): 454-64.

**13.** Perl AE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. *N Engl J Med* 2019; **381**(18): 1728-40. **14.** Daver N, et al. Targeting FLT3 mutations in AML: review of current knowledge and evidence. *Leukemia* 2019; **33**(2): 299-312. **15.** Dohner H, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017; **129**(4): 424-47. **16.** Intlekofer AM, et al. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. *Nature* 2018; **559**(7712): 125-9.