# Rapid Acute Myeloid Leukemia Targeted Therapy Mutation Panel

Last Literature Review: March 2024 Last Update: June 2024

Acute myeloid leukemia (AML) is a clonal disorder of hematopoietic progenitor cells. Recent studies have identified recurrently mutated genes with diagnostic, prognostic, and therapeutic significance in AML. The presence of certain variants may inform clinical management.

This multigene panel can be used upon initial diagnosis or overt relapse of AML to assess molecular changes, including single nucleotide variants (SNVs) and small insertions and deletions (indels) in select hotspots of relevant genes via massively parallel sequencing (MPS; also referred to as next generation sequencing [NGS]). This test has a fast turnaround time, which is critical in the timely identification of prognostic markers and advantageous in immediate patient management. In addition, it is more cost-effective than the use of multiple single gene tests and can be used to complement the morphologic and cytogenetic workup of AML. For testing for subsequent or more comprehensive analyses, refer to the Myeloid Malignancies Mutation and Copy Number Variation Panel by Next Generation Sequencing Test Fact Sheet.

This test is NOT intended to detect minimal residual disease (MRD).

## Featured ARUP Testing

Rapid Acute Myeloid Leukemia Targeted Therapy Mutation Panel 3017050

**Method:** Massively Parallel Sequencing

For more information on ARUP's myeloid malignancies panel, which includes the genes in this panel and additional genes relevant to other myeloid malignancies, refer to the Myeloid Malignancies Mutation and Copy Number Variation Panel by Next Generation Sequencing Test Fact Sheet.

For information on other ARUP tests relevant to AML, including information on single-gene tests, refer to the Acute Myeloid Leukemia Molecular Genetic Testing Test Fact Sheet.

# Disease Overview

## Diagnostic, Prognostic, and Treatment Issues

Identification of one or more clonal genetic abnormalities, variants, or patterns of variants in patients with AML may:

- Aid in establishing the diagnosis of certain subtypes of AML
- Aid in the determination of prognosis and identification of therapeutic targets
- Inform clinical management

# Genetics

## Genes Tested

**Rapid Acute Myeloid Leukemia Targeted Therapy Mutation Panel: Genes Tested**

| Gene | Transcript (NM) | Covered Exon(s) | Covered Region(s) |
|---|---|---|---|
| *CEBPA* | NM_004364 | 1 | chr19:33792244-33793320 |
| *FLT3* | NM_004119 | 14, 15, 16, 20 | chr13:28608209-28608361<br>chr13:28608014-28608138<br>chr13:28602305-28602435<br>chr13:28592594-28592736 |
| *IDH1* | NM_005896 | 4[a] | chr2:209113083-209113292 |
| *IDH2* | NM_002168 | 4 | chr15:90631809-90631984 |
| *KIT* | NM_000222 | 8, 9, 10, 11, 17 | chr4:55589740-55589874<br>chr4:55592023-55592226<br>chr4:55593374-55593500<br>chr4:55593572-55593718 |

| Gene | Transcript (NM) | Covered Exon(s) | Covered Region(s) |
|---|---|---|---|
| | | | chr4:55599226-55599368 |
| *KRAS* | NM_004985 | 2, 3, 4 | chr12:25398198-25398318<br>chr12:25380158-25380356<br>chr12:25378538-25378717 |
| *NPM1* | NM_002520 | 11[a] | chr5:170837521-170837569 |
| *NRAS* | NM_002524 | 2, 3, 4 | chr1:115258661-115258781<br>chr1:115256411-115256609<br>chr1:115252180-115252359 |
| *TP53* | NM_000546 | All coding (noncoding exon 1 is not covered) | chr17:7579837-7579912<br>chr17:7579690-7579731<br>chr17:7579302-7579600<br>chr17:7578361-7578564<br>chr17:7578167-7578290<br>chr17:7577489-7577615<br>chr17:7577009-7577165<br>chr17:7576843-7576936<br>chr17:7573917-7574043<br>chr17:7572926-7573017 |

[a]Indicated exons are partially targeted (for hotspots only) and not reportable in full.

# Test Interpretation

## Results

Reported variants are classified into two categories:

- Variants with known clinical significance in hematologic malignancies
- Variants of unknown clinical significance in hematologic malignancies

## Limitations

### Variants Not Detected

- Some variants may not be identified due to technical limitations in the presence of pseudogenes, in GC-rich regions, in repetitive or homologous regions, or in regions overlapping with primers designed for target enrichment.
- Variants at exon-intron boundaries may not be detected.
- Variants in regions that are not included in the targeted coding regions of the preferred transcript for the targeted genes
- Copy number variants (losses or gains)
- Loss of heterozygosity
- RNA variants
- Gene fusions, balanced translocations, and other structural variants

### Variants Not Reported

- Benign or likely benign variants in the preferred transcript
- Variants other than hotspot mutations may not be reported

### Additional Limitations

- This test is not intended to detect MRD.
- Interpretation of this test result may be impacted if this patient has had an undisclosed allogeneic bone marrow transplant or stem cell transplant.
- This test does not distinguish between somatic and germline variants

## Limit of Detection

- SNVs and small variants <25 base pairs (bp): 5% variant allele fraction (VAF)
  - Variants >25 bp: may be detected at limit of detection (LOD), but analytic sensitivity may be reduced
- *FLT3* internal tandem duplications (ITDs) (3-126bp): 10% VAF

## Analytic Sensitivity

| Variant Class | Analytic Sensitivity (PPA)[a] Estimate (%) | Analytic Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | 98.9 | 95.2-99.8 |
| Insertions/duplications/MNVs (1-25bp) | 100 | 96.2-99.9 |
| FLT3 ITDs | 97.7 | 90.0-99.7 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; ITDs, internal tandem duplications; MNVs, multinucleotide variants; PPA, positive percent agreement

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