

Myeloid Malignancies Mutation and Copy Number Variation Panel by Next Generation Sequencing

Content Review: August 2023 Last Update: January 2024

Myeloid malignancies are clonal disorders of hematopoietic stem and progenitor cells that include myelodysplastic syndromes (MDSs), myeloproliferative neoplasms (MPNs), myelodysplastic/myeloproliferative neoplasms (MDS/MPNs), acute myeloid leukemia (AML), and others. Recent studies have identified recurrently mutated genes with diagnostic, prognostic, and therapeutic impact in myeloid malignancies. The presence of certain variants may inform clinical management.

ARUP's Myeloid Malignancies Mutation and Copy Number Variation Panel by Next Generation Sequencing (3016621) uses massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) to detect molecular changes (single nucleotide variants [SNVs], small insertions and deletions), copy number variants (CNVs) for the targeted genes, and terminal copy number-neutral loss of heterozygosity (CN-LOH). Myeloid Malignancies Mutation Panel by Next Generation Sequencing (2011117) uses massively parallel sequencing to detect molecular changes including SNVs and small insertions and deletions but does not detect CNVs or CN-LOH. Because these panels overlap, they should not be concurrently ordered. If both panels are ordered on the same specimen, 2011117 will be canceled

These tests are more cost-effective than multiple single gene tests for the detection of somatic variants in myeloid malignancies and can be used to complement the morphologic and cytogenetic workup of myeloid malignancies.

Featured ARUP Testing

Myeloid Malignancies Mutation and Copy Number Variation Panel by Next Generation Sequencing 3016621

Method: Massively Parallel Sequencing

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117

Method: Massively Parallel Sequencing

For more information on ARUP's AML panel, which tests a subset of the genes in this panel specific to AML, refer to the Acute Myeloid Leukemia Mutation Panel by Next Generation Sequencing Test Fact Sheet.

For more information on ARUP's genomic microarray test offerings in oncology, refer to the Cytogenomic Microarray - Oncology Test Fact Sheet

Disease Overview

Diagnostic, Prognostic, and Treatment Issues

- Targets in this panel are relevant across the spectrum of myeloid malignancies.
- Identification of one or more clonal genetic abnormalities, variants, or patterns of variants may aid in establishing the diagnosis and classification, prognosis, and clinical management of myeloid malignancies.

Genetics

Genes Tested

ANKRD26, ASXL1, ASXL2, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CEBPA, CSF3R, CUX1, DDX41, DNMT1, DNMT3A, ELANE, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, HNRNPK, IDH1, IDH2, IL7R, JAK1, JAK2, JAK3, KDM6A, KIT, KMT2A, KRAS, LUC7L2, MPL, NOTCH1, NPM1, NRAS, NSD1, PHF6, PIGA, PPM1D, PRPF40B, PRPF8, PTPN11, RAD21, RUNX1, SAMD9, SAMD9L, SETBP1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAT3, STAT5B, SUZ12, TET2, TP53, U2AF1, U2AF2, UBA1, WT1, ZRSR2

For some genes, one or more exons of the preferred transcript are not covered by sequencing for the indicated gene. Refer to the Genes Tested table below for full list of targeted regions and exclusions.

Test Interpretation

Results

- Variant classifications:
 - o Tier 1: Molecular mutations, CNVs, and CN-LOH with known clinical significance in hematologic malignancies
 - Tier 2: Variants of unknown clinical significance in hematologic malignancies
 - Clinical significance in hematologic malignancies will be described, if known.

Reported Variants

	Myeloid Malignancies Mutation and Copy Number Variation Panel by Next Generation Sequencing (3016621)	Myeloid Malignancies Mutation Panel by Next Generation Sequencing (2011117)		
Reported	Sequence variants in the preferred transcript	Sequence variants in the preferred		
	CNVs (gains or losses) in the targeted genes	transcript		
	Likely acquired terminal CN-LOH			
	CNVs ≥5 Mb in any gene			
	Losses in TBL1XR1, CD200, IKZF1, CDKN2A, ASMTL, ERG, ARID2, ATM			
	Gains in MYC			
	Losses between FIP1LI and PDGFRA that result in a potential fusion Any CN-LOH involving TP53, JAK2, and CBL			
Not	Benign or likely benign variants	Benign or likely benign variants		
reported	Likely germline or interstitial CN-LOH	CNVs		
	Due to the complexity of analysis, CNVs may not be reported in instances of stem cell transplants that present with mixed chimerism, increased genomic complexity (>4 CNVs), and complex aneuploidies (eg, hyper- or hypodiploidy)	CN-LOH		
	VAF for CNVs with copy number >3			

Mb, megabases; VAF, variant allele fraction

Limitations

- · Variants may not be identified due to technical limitations in the presence of pseudogenes or in repetitive or homologous regions.
- · Not intended to detect minimal residual disease (MRD).
- Interpretation may be impacted if the patient has had an undisclosed allogeneic bone marrow or stem cell transplant.
- Does not distinguish between somatic and germline variants.
- The Myeloid Malignancies Mutation and Copy Number Variation Panel by Next Generation Sequencing (3016621) does not replace conventional cytogenetic studies or genomic microarray in the workup of hematologic malignancies.
- Neither panel detects the following types of variants:
 - Variants in regions that are not included in the preferred transcript for the targeted genes; refer to the Genes Tested table
 - RNA variants
 - Gene fusions, balanced translocations, and other structural variants

Limit of Detection

- SNVs and variants <24 bp: 5% VAF
 - Variants >24 bp may be detected at limit of detection (LOD), but analytic sensitivity may be reduced.
- CNVs (gains and losses): >2 Mb in approximately 30% of the sample
- CN-LOH: >10 Mb in approximately 30% of the sample
 - Some areas of the genome may have a reduced sensitivity for CNVs and CN-LOH at LOD.

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) ^a Estimate (%)	Analytic Sensitivity (PPA) 95% Credibility Region ^a (%)
SNVs	96.9	95.1-98.1
Insertions/duplications (1-24 bp)	98.1	95.5-99.3
Insertions/duplications (>24 bp)	>99	92.9-100.0
Deletions (1-24 bp)	96.7	92.8-98.7

^aGenes 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

Variant Class	Analytic Sensitivity (PPA) ^a Estimate (%)	Analytic Sensitivity (PPA) 95% Credibility Region ^a (%)
Deletions (>24 bp)	90	79.5-96.1
MNVs	97	93.0-99.0
FLT3 ITDs	>99	97.1-100.0
Copy number gains (>2 Mb)	91.8	86.7-95.3
Copy number losses (>2 Mb)	92.3	87.7-95.5
Copy number-neutral LOH (>10 Mb)	98.1	91.5-99.8

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

Genes Tested

Gene	Preferred Transcript ^a	Excluded Exons ^b
ANKRD26	NM_014915	-
ASXL1	NM_015338	-
ASXL2	NM_018263	-
BCOR	NM_001123385	-
BCORL1	NM_021946	-
BRAF	NM_004333	-
CALR	NM_004343	-
CBL	NM_005188	-
CBLB	NM_170662	-
CEBPA	NM_004364	-
CSF3R	NM_156039	-
CUX1	NM_181552	24
DDX41	NM_016222	-
DNMT1	NM_001130823	5
DNMT3A	NM_175629	-
ELANE	NM_001972	-

^aThis is the transcript number used for analyzing and reporting variants. The transcript version number may change periodically and thus is not listed here. The transcript with version number will be included on the patient's report if a variant is detected in the gene.

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

^bNoncoding exons are not analyzed, except for regions containing known clinically relevant variants in the ANKRD26 5'UTR and NOTCH1 3'UTR. In addition, coding exons noted here are not sequenced due to technical limitations of the assay.

ETNR1 NNL.0018838 — ETVR NNL.004898 — ESTRIT NNL.004898 — ESTRIT NNL.004119 — CATAT NNL.002049 — GAYAZ NNL.002168 — GNAS NNL.002169 — INMRPR NNL.002160 — IDM2 NNL.002180 — LIVIR NNL.002181 — LIVIR NNL.002185 — JAKZ NNL.002181 — JAKZ NNL.002191 — KAMA NNL.002191 — KAMA NNL.002191 — KAMA NNL.00191/101 —	Gene	Preferred Transcript ^a	Excluded Exons ^b
EXIV NML004456 — FBXVV NML003692 — FXX3 NML002119 — CATA1 NML002049 — GATA2 NML002888 — GNAS NML002140 — IDH1 NML002140 — IDH2 NML002168 — ILZR NML002185 — JAK1 NML002227 — JAK2 NML0049372 — JAK3 NML00219141S 13 KWT NML00191104 — KWTA2A NML00199104 — KWAS NML00199104 — KWAS NML016119 — KWAS NML016019 — MOTCH1 NML002520 1 NPMT NML002524 — NPMT NML002534 — NRAS NML002534 —	ETNK1	NM_018638	-
FEXIVAT NNAL.033832 - FLT3 NNAL.004119 - GATAT NNAL.002049 - GATAZ NNAL.002688 - GNAS NNAL.002160 - IDHT NNAL.002160 - IDHZ NNAL.002185 - ILTR NNAL.002185 - JAKT NNAL.00217 - JAKG NNAL.002181 - KDM6A NNAL.00219415 - KDM6A NNAL.001291415 - KM7ZA NNAL.001291415 - KM7ZA NNAL.001291415 - KWAS NNAL.00197104 - KWAS NNAL.00197104 - KWAS NNAL.005973 - NOTCHT NNAL.005213 - NPMT NNAL.005252 - NNAL NNAL.005252 - NNAL NNAL.005252 -	ETV6	NM_001987	-
FIT3 NNA_004119 - CATAT NNA_002049 - GATAZ NNA_002688 - GMAS NNA_000516 - IDHT NNA_002140 - IDHT NNA_002168 - IL7R NNA_002185 - JAKT NNA_002227 - JAKZ NNA_004972 - JAKR3 NNA_000215 - KOM6A NNA_00129141S 3 KWT NNA_00022 - KMTZA NNA_00197104 - KWTAS NNA_00498S - LUC7L2 NNA_005373 - MPL NNA_005373 - NOTCHT NNA_005224 - NPMI NNA_005254 - NNA NNA_002545 -	EZH2	NM_004456	-
GATA1 NM_002049 — GATA2 NM_002588 — GNAS NM_000516 — INHRIPK NM_002140 — IDH1 NM_005896 — IDH2 NM_002188 — JAK7 NM_002185 — JAK2 NM_004972 — JAK3 NM_004972 — KDM6A NM_00129115 13 KVT NM_00129115 13 KWT2A NM_00129115 — KWT2A NM_00129110 — KWT2A NM_00197104 — KWTAS NM_005373 — KWT NM_005373 — NOTOHT NM_00520 1 NPM1 NM_002520 1 NRAS NM_002524 — NBAD NM_002545 —	FBXW7	NM_033632	-
GATA2 NM.032638 - GNAS NM.00516 - HNRNPK NM.002140 - IDH1 NM.005896 - IDH2 NM.002168 - IL7R NM.002185 - JAK7 NM.002227 - JAK2 NM.004972 - JAK3 NM.002151 - KT NM.00222 - KMT NM.00222 - KMTZA NM.001931415 13 KRAS NM.001197104 - KRAS NM.004985 - LUC7L2 NM.016619 - MPL NM.005373 - NOTCH1 NM.005373 - NPM1 NM.002520 1 NPM3 NM.002524 - NB01 NM.002524 -	FLT3	NM_004119	-
GNAS NML000516 - HNRNPK NML002140 - IDH1 NML005896 - IDH2 NML002168 - IL7R NML002185 - JAK1 NML002227 - JAK2 NML000215 - KDM6A NML00191415 13 KIT NML00197104 - KMT2A NML00197104 - KRAS NML00197104 - LUC7L2 NML001619 - APL NML0068373 - NOTOH1 NML002520 1 NPM1 NML002524 - NPM2 NML002524 - NPM3 NML002525 -	GATA1	NM_002049	-
HNRNPK NM_002140 - IDH1 NM_002168 - IDH2 NM_002168 - IL7R NM_002185 - JAK7 NM_00472 - JAK3 NM_00472 - KDM6A NM_001291415 13 KIT NM_00222 - KMTZA NM_001197104 - KRAS NM_001197104 - LUC7L2 NM_016019 - MPL NM_05373 - NPM1 NM_052520 1 NPM1 NM_002520 1 NBAS NM_022455 -	GATA2	NM_032638	-
IDH1 IML005896 - IDH2 IML002168 - ILTR IML002185 - JAK1 IML002227 - JAK2 NML004972 - KDM6A NML001591415 3 KT NML000222 - KMTZA NML001197104 - KRAS NML004985 - LUCZL2 NML016019 - NPM1 NML005373 - NPM1 NML017617 - NPM1 NML002520 1 NRAS NML002524 - NSD1 NML002455 -	GNAS	NM_000516	-
IDH2 NM_002168 - ILTR NM_002185 - JAK1 NM_002227 - JAK2 NM_004972 - KDM6A NM_001591415 - KIT NM_000222 - KMT2A NM_001197104 - KRAS NM_004985 - LUC7L2 NM_016019 - NPUT NM_005373 - NPW1 NM_017617 - NPW1 NM_002520 1 NRAS NM_002524 - NSD1 NM_002524 -	HNRNPK	NM_002140	-
LTR NM_002185 - JAK1 NM_002227 - JAK2 NM_004972 - JAK3 NM_000215 - KDM6A NM_001291415 13 KMT 2A NM_000222 - KMT2A NM_001197104 - KRAS NM_016019 - LUC7L2 NM_016019 - NOTCH1 NM_005373 - NPM1 NM_002520 1 NPAS NM_002524 - NSD1 NM_002545 -	IDH1	NM_005896	-
JAK1 NM_002227 — JAK2 NM_004972 — JAK3 NM_000215 — KDM6A NM_001291415 13 KIT NM_000222 — KMT2A NM_001197104 — KRAS NM_004985 — LUC712 NM_016019 — MPL NM_005373 — NOTCH1 NM_017617 — NPM1 NM_002520 1 NRAS NM_002524 — NSD1 NM_02455 —	IDH2	NM_002168	-
JAK2 NM_004972 - JAK3 NM_000215 - KDM6A NM_01291415 13 KIT NM_000222 - KMT2A NM_01197104 - KRAS NM_004985 - LUC7L2 NM_016019 - MPL NM_05373 - NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	IL7R	NM_002185	-
JAK3 NM_000215 - KDM6A NM_001291415 13 KIT NM_000222 - KMT2A NM_001197104 - KRAS NM_004985 - LUC7L2 NM_016019 - MPL NM_005373 - NPM1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	JAK1	NM_002227	-
KDM6A NM_001291415 13 KIT NM_000222 - KMT2A NM_001197104 - KRAS NM_004985 - LUC7L2 NM_016019 - MPL NM_005373 - NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	JAK2	NM_004972	-
KIT NM_000222 - KMT2A NM_001197104 - KRAS NM_004985 - LUC7L2 NM_016019 - MPL NM_005373 - NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	JAK3	NM_000215	-
KMT2A NM_001197104 - KRAS NM_004985 - LUC7L2 NM_016019 - MPL NM_005373 - NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	KDM6A	NM_001291415	13
KRAS NM_004985 - LUC7L2 NM_016019 - MPL NM_005373 - NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	KIT	NM_000222	-
LUC7L2 NM_016019 - MPL NM_005373 - NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	КМТ2А	NM_001197104	-
MPL NM_005373 - NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	KRAS	NM_004985	-
NOTCH1 NM_017617 - NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	LUC7L2	NM_016019	-
NPM1 NM_002520 1 NRAS NM_002524 - NSD1 NM_022455 -	MPL	NM_005373	-
NRAS NM_002524 - NSD1 NM_022455 -	NOTCH1	NM_017617	-
NSD1 NM_022455 —	NPM1	NM_002520	1
	NRAS	NM_002524	-
PHF6 NM_001015877 –	NSD1	NM_022455	-
	PHF6	NM_001015877	-

^aThis is the transcript number used for analyzing and reporting variants. The transcript version number may change periodically and thus is not listed here. The transcript with version number will be included on the patient's report if a variant is detected in the gene.

^bNoncoding exons are not analyzed, except for regions containing known clinically relevant variants in the ANKRD26 5'UTR and NOTCH1 3'UTR. In addition, coding exons noted here are not sequenced due to technical limitations of the assay.

Gene	Preferred Transcript ^a	Excluded Exons ^b
PIGA	NM_002641	-
PPM1D	NM_003620	-
PRPF8	NM_006445	-
PRPF40B	NM_001031698	-
PTPN11	NM_002834	-
RAD21	NM_006265	-
RUNX1	NM_001754	-
SAMD9	NM_017654	-
SAMD9L	NM_152703	-
SETBP1	NM_015559	-
SF3B1	NM_012433	-
SH2B3	NM_005475	-
SMC1A	NM_006306	-
SMC3	NM_005445	-
SRSF2	NM_003016	-
STAG2	NM_001042749	-
STAT3	NM_139276	-
STAT5B	NM_012448	6-9
SUZ12	NM_015355	1-9
TET2	NM_001127208	-
TP53	NM_000546	-
U2AF1	NM_006758	-
U2AF2	NM_007279	-
UBA1	NM_003334	-
WT1	NM_024426	-
ZRSR2	NM_005089	-
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Related Information

Acute Myeloid Leukemia - AML Myelodysplastic Syndromes Myeloproliferative Neoplasms - MPNs

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