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

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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 panels, which include some of the genes in this panel specific to AML, refer to the Acute Myeloid Leukemia Mutation Panel by Next Generation Sequencing and Rapid Acute Myeloid Leukemia Targeted Therapy Mutation Panel Test Fact Sheets.

For detection of sequence variants in the *TP53* gene alone, see Somatic *TP53* Mutations in Whole Blood and Bone Marrow 3017691.

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:
  - 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 CNVs (gains or losses) in the targeted genes 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*	Sequence variants in the preferred transcript
Not reported	Benign or likely benign variants Likely germline or interstitial CN-LOH 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) VAF for CNVs with copy number >3	Benign or likely benign variants CNVs CN-LOH

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
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

[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

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	—
ETNK1	NM_018638	—
ETV6	NM_001987	—
EZH2	NM_004456	—

Gene	Preferred Transcript[a]	Excluded Exons[b]
FBXW7	NM_033632	–
FLT3	NM_004119	–
GATA1	NM_002049	–
GATA2	NM_032638	–
GNAS	NM_000516	–
HNRNPK	NM_002140	–
IDH1	NM_005896	–
IDH2	NM_002168	–
IL7R	NM_002185	–
JAK1	NM_002227	–
JAK2	NM_004972	–
JAK3	NM_000215	–
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	–
PHF6	NM_001015877	–
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	–

Gene	Preferred Transcript[a]	Excluded Exons[b]
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[c]	NM_000546	—
U2AF1	NM_006758	—
U2AF2	NM_007279	—
UBA1	NM_003334	—
WT1	NM_024426	—
ZRSR2	NM_005089	—

[a] This 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.

[b] Noncoding 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.

[c] For detection of sequence variants in the *TP53* gene alone, see Somatic *TP53* Mutations in Whole Blood and Bone Marrow 3017691.