Gennext

This genomic analysis report contains the results of tests performed at {Clinic Name} laboratory. The report infrastructure and bioinformatics analysis platform are provided by Gennext.

AML
Clinical Diagnosis

01-01-1111
Pathology Report Date

#########
Specimen Type

#########
Specimen Site

#######
Test Panel

01-01-1111
Test Report Date

#########
Referring Center

#########
Referring Doctor

Patient Name
Patient Name & Surname

01-01-1111
Date of Birth

BIOMARKER FINDINGS

TMB Level **9.4**
Tumor Mutational Burden

MSI Status **MSI-H**
Count: 100/40
Percentage: %40

HRD Status **Negative**
BRCA1/2: WT
GSS: 8

ACTIONABLE VARIANTS

Gene	Finding	VAF	Tier	Relevant Therapies	Cancer Type	Clinical Trials
FLT3 NM_004119.3	c.1818_1819insGAATATGATCTCAAATGG GAGTTTCCAp.R607delinsEYDLKWEFPR	44.1%	Tier I	Quizartinib, Gilteritinib, Midostaurin + High Dose Chemotherapy	AML	ⓘ
NPM1 NM_002520.7	c.859_860insTCTG(p.W288Cfs*12)	47.1%	Tier I	Revumenib	No	ⓘ
DNMT3A NM_022552.5	c.2644C>T(p.R882C)	44.5%	Tier II	No	No	ⓘ

CLINICAL TRIALS

No clinical trials found in this sample.

OTHER VARIANTS

No other variants found in this sample.

ACTIONABLE VARIANTS - DETAILED

Gene	Variant Interpretation	VAF	DNA Alteration	Protein Alteration	Cancer Type	Clinical Trials
FLT3 NM_004119.3	TIER I	44.1%	c.1818_1819insGAATATGATC	p.R607delinsEYDLKWEFPR	AML (Acute Myeloid Leukemia)	ⓘ

Gene Description

FLT3, a receptor tyrosine kinase, is recurrently altered in acute myeloid leukemia and other hematologic malignancies.

Variant Interpretation:

Tier I
The FLT3 internal tandem duplication is known to be **oncogenic**.

Mutation Effect: FLT3 internal tandem duplications (ITDs) are located in either the juxtamembrane domain and/or the tyrosine kinase domain of the protein. These mutations have been found in acute myeloid leukemia (AML) (PMID: 23631653). Expression of these mutations in murine bone marrow, murine B-cell and simian fibroblast cells lines and in an in vivo bone marrow transplant model demonstrated that they are activating, as measured by increased growth factor-independent proliferation and the induction of an in vivo myeloproliferative phenotype compared to wildtype (PMID: 11756186, 23631653, 9737679, 11090077, 12384447). Analysis of patients with AML harboring these mutations demonstrated that expression of ITDs that were composed of exogenous sequence in the wildtype FLT3 sequence were more likely to respond favorably to treatment with either chemotherapy or FLT3 tyrosine kinase inhibitors as compared to patients expressing FLT3 ITDs composed of exogenous sequence in between the duplication (PMID: 30181385).

Gene	Variant Interpretation	VAF	DNA Alteration	Protein Alteration	Cancer Type	Clinical Trials
NPM1 NM_002520.7	TIER I	47.1%	c.859_860insTCTG	p.W288Cfs*12	AML (Acute Myeloid Leukemia)	ⓘ

Gene Description

NPM1, a nucleolar phosphoprotein, is frequently altered in hematologic malignancies.

Variant Interpretation:

Tier I
The NPM1, Trp288Cysfs*12 mutation is known to be **oncogenic**.

Mutation Effect: NPM1, also known as nucleophosmin, is a nucleolar phosphoprotein that has diverse cellular functions including regulation of ribosome biogenesis, mRNA processing, chromatin remodeling, apoptosis and DNA damage repair (PMID: 16007073). NPM1 has been implicated in the regulation of several DNA repair processes including homologous recombination, translesion synthesis, and repair of lesions created by UV light (PMID: 27553022). Loss of NPM1 has also been associated with increased genome instability (PMID: 16007073). In addition, NPM1 plays an important role in the regulation of the TP53 tumor suppressor pathway. The TP53-stabilizing protein ARF binds NPM1, sequestering ARF and NPM1 from binding the ubiquitin ligase MDM2 that is responsible for degrading TP53. Disruption of the NPM1-ARF interaction allows NPM1 and ARF to inhibit MDM2-mediated degradation of p53 leading to apoptosis (PMID: 15144954,15684379). Translocations and loss-of-function mutations have been identified in various human lymphomas and leukemias (PMID: 15659725, 8122112, 17488663). Mutations in NPM1 commonly result in a cytoplasmic form, NPM1c, which functions as a dominant negative and excludes NPM1 from the nucleus. NPM1c mutations in acute myeloid leukemia have been associated with a more favorable patient prognosis (PMID: 15659725). Murine models engineered to express NPM1 mutations develop hematopoietic disease and cooperate with other oncogenes to induce leukemias (PMID: 26559910). In solid tumors, NPM1 is commonly overexpressed leading to mislocalization of NPM1 (PMID: 26559910, 21258971,18037965, 26559910).

Gene	Variant Interpretation	VAF	DNA Alteration	Protein Alteration	Cancer Type	Clinical Trials
DNMT3A NM_022552.5	TIER II	44.5%	c.2644C>T	p.R882C	AML (Acute Myeloid Leukemia)	ⓘ

Gene Description

DNMT3A, a tumor suppressor and DNA methyltransferase, is recurrently mutated in acute myeloid leukemia and other hematologic malignancies.

Variant Interpretation:

Tier II
The DNMT3A R882C mutation is known to be **oncogenic**.

Mutation Effect: The DNMT3A R882C mutation is located in the methyltransferase domain of the DNMT3A protein. This mutation has been found recurrently in leukemias (PMID: 24656771). In vitro studies have demonstrated that this mutation is inactivating as measured by reduced methyltransferase activity, enhanced hypomethylation, and altered chromatin remodeling activity compared to wildtype (PMID: 24656771, 27010235, 27841873). Drug efficacy studies have demonstrated that the R882C mutation may confer resistance to DNA methyltransferase inhibitors and other cytotoxic chemotherapies (PMID: 27841873, 30291338).

METHODOLOGY & BIOMARKER DEFINITIONS

TMB (Tumor Mutational Burden)
TMB refers to the number of mutations present within a tumor's DNA. It quantifies the total number of mutations per coding area of a tumor genome. A higher TMB often indicates a greater likelihood of the tumor responding to certain immunotherapies. The rationale is that tumors with more mutations might produce more neoantigens, which can be recognized by the immune system as foreign, making them potentially more susceptible to immune checkpoint inhibitors.

MSI (Microsatellite Instability)
MSI is a condition that arises due to defects in the DNA mismatch repair system. When this system is defective, errors that naturally occur during DNA replication aren't corrected, leading to the accumulation of mutations, particularly in microsatellite regions of the genome. Tumors with high MSI (often denoted as MSI-H) have a large number of mutations and, like those with high TMB, may be more receptive to certain immunotherapies.

HRD (Homologous Recombination Deficiency)
HRD refers to a deficiency in the homologous recombination DNA repair pathway. Tumors with HRD are characterized by impaired ability to repair double-strand DNA breaks, leading to genomic instability. HRD tumors may be more sensitive to PARP inhibitors and platinum-based chemotherapies.

Methodology
A capture based targeted next generation sequencing (NGS) analysis was performed, using the SureSelect Cancer CGP Assay (Agilent) which is a qualitative in vitro diagnostic test.

89	N/A	N/A	N/A
Genes (DNA)	Genes (RNA)	Complete Exons	Biomarkers

Sensitivity & Specificity

Sensitivity 100%
Positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs)

Specificity: 100%
Negative percent agreement (NPA) for SNVs, Indels, fusions and CNVs

GENE PANEL CONTENT

CNVs (25+ genes)

ABL1	ARID1A	ASXL1	ARID1B	ATM	ATRX	B2M	BCL2	BCL6	BCOR
BCORL1	BRAF	BTK	CALR	CBL	CARD11	CCND1	CD79A	CD79B	CDKN2A
CEBPA	CRBN	CREBBP	CSF3R	CSF1R	CUL4B	CXCR4	DDX3X	DIS3	DNMT3A
EGFR	EGR2	EP300	ETV6	EZH2	FAS	FBXW7	FLT3	FOXO1	GATA1
GATA2	GNA13	GNAS	HRAS	ID3	IDH1	IDH2	IKZF1	IKZF3	IRF4
JAK2	JAK3	JUNB	KDM6A	KIT	KMT2D	KRAS	MAP2K1	MPL	MYC
MYD88	NOTCH1	NOTCH2	NPM1	NRAS	PAX5	PDGFRA	PHF6	PIK3CA	PIM1
PLCG2	PTEN	RPS15	RUNX1	SAMHD1	SETBP1	SF3B1	SMARCA4	SMC1A	SMC3
STAT3	STAT5B	TCF3	TET2	TNFRSF14	TP53	TRAF3	UBA1	WT1	XBP1

DISCLAIMER AND LIMITATIONS

Disclaimer

- This test is mainly used to assist clinical decision-making and the result does not represent clinical decision.
- The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
- The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: **https://clinicaltrials.gov/.**
- As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
- Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follows guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).

Guidelines Followed: ACMG • AMP • ASCO • CAP

Database and References Used:

Reference genome (GRCh38) • LRG annotation • 1000G (phase3II-nonc) • ExAC (0.3.1) • dbSNP (147) • PolyPhen2/SIFT (ensdb v73) • PhyloP (2013-12-06) • ClinVar (2018-8) • Cosmic(V85) • OncoKB v1.4.0

Limitations

- The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
- Limited tissue detection may not represent the whole DNA variations of lesions because of tumor heterogeneity.
- Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
- Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
- The detection could not distinguish between somatic mutations and germline mutations effectively without control sample analysis.
- Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation.

Quality Metrics

Base Quality ≥ Q30: The proportion of base quality in sequencing data that reaches or exceeds Q30, indicating that the probability of base recognition accuracy rate exceeds 99.9%.