

Patient ID 321	Patient Name TESTRNV, IMPLEMENTATION	Birth Date 1970-11-13	Gender M	Age 47
Order Number X100264925	Client Order Number X100264925	Ordering Physician CLIENT, CLIENT	Report Notes	
Account Information C7028846 DLMP Rochester		Collected 22 Aug 2018 12:25		

NGS for Myeloid Neoplasms (NGSHM)

Specimen Type

Bone Marrow

MCR

Indication for Test

AML

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Pathogenic Mutations Detected

1. ASXL1: Chr20(GRCh37):g.31022415_31022437del;
NM_015338.5(ASXL1):c.1900_1922del; p.Glu635Argfs*15 (45%)

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Note: Genetic Alterations with FDA-Approved Therapies for Acute Myeloid Leukemia FLT3: Not Detected IDH2: Not Detected

No other pathogenic mutations were detected in the other genes tested on the panel at the reportable limit of assay detection. See below for Variants of Unknown Significance and Additional Notes. Please see the section of "Panel Gene List" below for the complete list of genes tested.

Interpretation

1. ASXL1: Chr20(GRCh37):g.31022415_31022437del;
NM_015338.5(ASXL1):c.1900_1922del; p.Glu635Argfs*15

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Normal gene/protein function: The ASXL1 gene (additional sex combs like 1) located at chromosome 20q11.21 encodes a chromatin-binding protein required for normal embryonic segmentation and regulates epigenetic marks and transcription. ASXL1 interacts with the polycomb repressive complex 2 (PRC2) and regulates tri-methylation of histone H3 lysine 27 (H3K27me3), a chromatin modification process associated with gene silencing. It also associates with the deubiquitinating enzyme BAP1 and may promote expression of genes through removal of PRC1 complex-mediated H2A lysine 119 (H2AK119) ubiquitination (Abdel-Wahab et al., 2012, 22897849; Inoue et al., 2013, 24216483).

Mutation effect: The frameshift p.Glu635Argfs*15 mutation occurs before the highly conserved PHD domain and results in premature protein truncation; and is considered inactivating. Truncating mutations have been shown to result in decreased to absent expression of the wild-type ASXL1 protein, and are capable of inducing myelodysplastic syndrome-like disease in mouse models. In vitro assay shows markedly reduced H3K27 trimethylation genome-wide in hematopoietic cells following ASXL1 depletion. Loss of H3K27 tri-methylation promotes malignant transformation in hematopoietic cells (Abdel-Wahab et al., 2012, 22897849; Inoue et al., 2013, 24216483).

Disease associations: ASXL1 mutations have been reported in patients with a spectrum of myeloid malignancies including approximately 15–25% of myelodysplasia (MDS), 45% of chronic myelomonocytic leukemia (CMML), 10–15% of myeloproliferative neoplasm (MPN), 30% of secondary acute myeloid leukemia (s-AML) and 6.5% of de novo AML. Frameshift and nonsense mutations are associated with poor clinical outcome in myeloid neoplasms (Gelsi-Boyer et al., 2012, 22436456; Metzeler et al., 2011, 22031865; Pratcorona et al., 2012, 22058207; Thol et al., 2011, 21576631; Vannucchi et al., 2013, 23619563).

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

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Therapeutic implications: There are currently no targeted therapies for ASXL1 mutations. As ASXL1 mutations result in a loss of H3K27 trimethylation, inhibition of H3K27 demethylation has been suggested as a potential therapeutic approach in ASXL1-mutated myeloid neoplasm patients (Paschka et al., 2015, 25596267; Kruidenier et al., 2012, 22842901).

Variants of Unknown Significance

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None

The VUS variants listed here (with approximate variant allele %) are not sufficiently characterized in the current literature and are therefore of uncertain clinical significance at this time. They are reported here for future reference in the event they become clinically significant in the light of new scientific data.

Clinical Trials

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Information regarding possible clinical trials for this patient can be found at the following sites:

- 1). ClinicalTrials.gov:
<http://clinicaltrials.gov/ct2/search/advanced>
- 2). Mayo Clinic:
<http://www.mayo.edu/research/clinical-trials>
- 3). National Cancer Institute:
<http://www.cancer.gov/clinicaltrials/search>
- 4). Molecular Match:
<https://www.molecularmatch.com/>

Additional Notes

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None

Method Summary

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DNA is extracted from the peripheral blood or bone marrow sample and following library preparation by hybrid capture, subjected to next generation sequencing (NGS) with post-sequencing analysis of tumor-associated mutations. Because some regions in the target panel are not consistently resolved by NGS, additional separate clinical laboratory assays may also be used to complete the overall analysis including: CALR (CALR), CEBPA (CEBPA), CSF3R (CSF3R), FLT3 (FLT), JAK2 V617F Mutation Detection (JAK2B, JAK2M, or JAK2V), JAK2 Exon 12 Mutation Detection (JAKXB or JAKXM), KIT (KITB, KITBM, KITAS, or KITE), MPL (MPLB or MPLM), NPM1 (NPM1), and TP53 (P53CA).

Performance characteristics of NGS panel:

Single base substitutions: accuracy >99%; reproducibility 100% (intra- and interassay); sensitivity 5–10% variant allele fraction with a minimum depth coverage of 250X. Insertion/deletion events: accuracy >99%; reproducibility 100% (intra- and interassay); sensitivity 5–10% variant allele fraction with a minimum depth coverage of 250X.

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Disclaimer

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CLINICAL DISCLAIMER

Mutation calls detected between 5–10% variant allele fractions (VAF) may indicate low-level (i.e. subclonal) tumor populations, although the clinical significance of these findings may not be clear. Some apparent mutations classified as VUS may represent rare or low frequency polymorphisms. A low incidence of gene mutations associated with myeloid neoplasms can also be detected in hematopoietic cells with advancing age in some individuals without evidence of a hematologic malignancy ("clonal hematopoiesis") and these alterations may not be clearly distinguishable from tumor-associated mutations (PMID 25326804;25426838;25426837). Prior treatment for hematologic malignancy could affect the results obtained in this assay. In particular, prior allogeneic hematopoietic stem cell transplant (HSCT) may cause difficulties in resolving somatic or polymorphic alterations, or in assigning variant calls correctly to donor and recipient fractions, if pertinent clinical or laboratory information (e.g. chimerism engraftment status) is not provided. Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. This assay does not distinguish between somatic and germ line alterations in analyzed gene regions, particularly with VAF near 50% or 100%. If nucleotide alterations in genes associated with germ line mutation syndromes are present and there is also a strong clinical suspicion or family history of malignant disease predisposition, additional genetic testing and appropriate counseling may be indicated. This report interpretation is based on current medical and scientific literature, but clinical significance may not be completely established for all reported target gene abnormalities identified. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

TECHNICAL DISCLAIMER

The depth of sequencing coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria, or for failed regions are noted. Analysis of rare (low allele frequency) polymorphisms may be problematic in some cases. A low tumor cell percentage in the sample may affect the true mutation VAF and/or sensitivity. Suboptimal-performing regions (i.e. less than the expected minimum depth of coverage) may affect analytic sensitivity for detecting lower level mutations. This is a qualitative test. The variant read fractions are provided for information only and represent a relative proportion of mutated alleles, but do not indicate a measure of analytical sensitivity for the given genes; assay sensitivity is as stated in the method summary. Some genetic or genomic alterations, such as large insertion/deletion (indel) events, copy number alterations (CNA) and gene translocation events are not detected by this assay.

OncoHeme Panel Gene List

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ANKRD26 (NM_014915.2) 5'UTR, exons 1–4, intron c.172, ASXL1 (NM_015338.5) exons 10–13, BCOR (NM_001123385.1) exons 4–15, CALR (NM_004343.3) exon 9, CBL (NM_005188.3) intron 7 last 110bps before start of exon 8, exon 8, intron 8, CEBPA (NM_004364.4) exon 1, CSF3R (NM_000760.3) exons 14 and 17, DDX41 (NM_016222.2) exons 1–17, DNMT3A (NM_022552.4) exons 8–23, ELANE (NM_001972.2) exons 1–5, ETNK1 (NM_018638.4) exons 2–5, ETV6 (NM_001987.4) exons 3–8, EZH2 (NM_004456.4) exons 2–20, FLT3 (NM_004119.2) exons 14–20, GATA1 (NM_002049.3) exons 2 and 4, GATA2 (NM_001145661.1) exons 3–7, intron 5, c.1017+1–1017+730, IDH1 (NM_005896.3) exon 4, IDH2 (NM_002168.3) exon 4, JAK2 (NM_004972.3) exons 12–16, KDM6A (UTX) (NM_021140.3) exons 1–29, KIT (NM_000222.2) exons 8–11 and 17, KRAS (NM_033360.3) exons 2–3, MPL (NM_005373.2) exons 10–12, NPM1 (NM_002520.6) exons 9–11, to -30 before exon 11, NRAS (NM_002524.4) exons 2 and 3, PHF6 (NM_001015877.1) exons 2–10, PTPN11 (NM_002834.3) exons 3–4 and 12–13, RAD21 (NM_006265.2) exons 1, 2, 4–7, 9–11, 13, 14, exon 10 flank 15bp, RUNX1 (NM_001001890.2) exons 1–6, intron 4 c.725–13T>A and intron 5 c.886+1–4del, SETBP1 (NM_015559.2) partial exon 4; amino acids 400 - 950, SH2B3 (LNK) (NM_005475.2) exon 2–8, SF3B1 (NM_012433.2) exons 13–16, SRP72 (NM_006947.3) exons 6, 10, SMC3 (NM_005445.3) exons 7, 8, 13, 17, 19, 21, 29, SRSF2 (NM_003016.4) exons 1 and 2, STAG2 (NM_001042750.1) exons 4–34, 12, 17 and 22 flank 15bp, TERT (NM_198253.2) exons 2–16, TET2 (NM_001127208.2) exons 3–11, TP53 (NM_000546.4) exons 4–9, U2AF1 (NM_001025203.1) exons 2, 6, and 8, WT1 (NM_024426.2) exons 1–10, and ZRSR2 (NM_005089.3) exons 1–11.

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For some genes, the transcript IDs used in this analysis may not be the same as in other cancer mutation databases, such as COSMIC (<http://cancer.sanger.ac.uk/cosmic>).

Reviewed By:

Signing Pathologist: BENJAMIN BAILEY

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NGSHM Result

See Interpretation

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Received: 23 Aug 2018 08:03

Reported: 23 Aug 2018 08:09

Test Environment
ETBB Template

Laboratory Notes

- 1 This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

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