Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: EXAMPLE, PHYSICIAN

Patient: Report, Example

DOB	4/26/2023
Sex:	Male
Patient Identifiers:	48329
Visit Number (FIN):	48682
Collection Date:	4/26/2023 07:37

Chronic Lymphocytic Leukemia Mutation Panel by Next Generation Sequencing

ARUP test code 3001858

Chronic Lymphocytic Leukemia Specimen	Whole Blood
Chronic Lymphocytic Leukemia Interp	See Note

See Note
CLL Panel by NGS

Submitted diagnosis or diagnosis under consideration for variant interpretation: Chronic lymphocytic leukemia (CLL)

TIER 1: Variants of Known Clinical Significance in Hematologic Malignancies

1. NOTCH1 c.7541_7542del, p.Pro2514fs (NM_017617.3)
VAF: 8.4%
NOTCH1 encodes a transmembrane receptor that functions as a transcription factor that regulates stem cell maintenance, cell differentiation, proliferation, and apoptosis (1) (10). NOTCH1 activating mutations occur in various hematologic malignancies including approximately 5-22% of chronic lymphocytic leukemia (CLL) patients (4) (11) (12) (13) (15). These mutations, most commonly Pro2514fs, are often
frameshift and nonsense mutations in the C-terminal heterodimerization (HD) and PEST domains as well as the 3' UTR of NOTCH1 (6). This particular frameshift mutation (Pro2514fs) is a recurrent activating mutation within the PEST domain (15). NOTCH1 activating mutations are associated with poor prognosis, including increased risk of progression and resistance to therapy in patients with CLL
(15).

2. KRAS c.38G>A, p.Gly13Asp (NM_004985.4)
VAF: 15.7%
The RAS genes (KRAS and NRAS) encode a family of membraneassociated signal-transduction proteins involved in regulating cell growth (2) (3). RAS mutations are found in a variety of hematologic malignancies including approximately 2-7% of patients with CLL (9) (14). These mutations predominantly occur at codons 12, 13, 61, 117 and 146, leading to activation of the RAS-ERK pathway (8) (9). This particular missense mutation has been reported in lymphoid malignancies (5). In CLL, one study concluded that RAS mutations were not associated with overall survival (7). Another study showed that RAS mutations were associated with shorter therapy-free survival and patients with KRAS mutations showed a higher incidence of somatic trisomy 12 (14). Correlation with cytogenetic findings is recommended.

TIER 2: Variants of Unknown Clinical Significance in Hematologic Malignancies

H=High, L=Low, *=Abnormal, C=Critical

None found

References
1: Arruga F, Gizdic B Serra S et al, Functional impact of NOTCH1 mutations in chronic lymphocytic leukemia. Leukemia 2014. PMID:24170027
2: Bowen DT, Frew ME, Hills R et al, RAS mutation in acute myeloid leukemia is associated with distinct cytogenetic subgroups but does not influence outcome in patients younger than 60 years. Blood 2005. PMID:15951308
3: Braun BS, Shannon K, Targeting Ras in myeloid leukemias. Clin Cancer Res 2008. PMID:18413813
4: cBioPortal: http://www.cbioportal.org/
5: COSMIC: https://cancer.sanger.ac.uk/cosmic
6: Fabbri G, Rasi S, Rossi D et al, Analysis of the chronic lymphocytic leukemia coding genome: role of NOTCH1 mutational activation. J Exp Med 2011. PMID:21670202
7: Gimenez N, Martinez-Trillos A Montraveta A et al Mutations in the RAS-BRAF-MAPK-ERK pathway define a specific subgroup of patients with adverse clinical features and provide new therapeutic options in chronic lymphocytic leukemia. Haematologica 2019. PMID:30262568
8: Hobbs GA, Der CJ, RAS Mutations Are Not Created Equal. Cancer Discov 2019. PMID:31160330
9: Landau DA, Tausch E, Taylor-Weiner AN et al, Mutations driving CLL and their evolution in progression and relapse. Nature 2015. PMID:26466571
10: Lobry C, Oh P, Aifantis I, Oncogenic and tumor suppressor functions of Notch in cancer: it's NOTCH what you think. J Exp Med 2011. PMID:21948802
11: Mansouri L, Cahill N, Gunnarsson R et al, NOTCH1 and SF3B1 mutations can be added to the hierarchical prognostic classification in chronic lymphocytic leukemia. Leukemia 2013. PMID:23138133
12: Nadeu F, Delgado J, Royo C et al, Clinical impact of clonal and subclonal TP53, SF3B1, BIRC3, NOTCH1, and ATM mutations in chronic lymphocytic leukemia. Blood 2016. PMID:26837699
13: Schnaiter A, Paschka P, Rossi M et al, NOTCH1, SF3B1, and TP53 mutations in fludarabine-refractory CLL patients treated with alemtuzumab: results from the CLL2H trial of the GCLLSG. Blood 2013. PMID:23821658
14: Vendramini E Bomben R Pozzo F et al KRAS NRAS and BRAF mutations are highly enriched in trisomy 12 chronic lymphocytic leukemia and are associated with shorter treatment-free survival. Leukemia 2019. PMID:30872781
15: Weissmann S, Roller A, Jeromin S et al, Prognostic impact and landscape of NOTCH1 mutations in chronic lymphocytic leukemia (CLL): a study on 852 patients. Leukemia 2013. PMID:23860447

This result has been reviewed and approved by [redacted]

Low coverage regions:
Listed below are regions where the average sequencing depth (number of times a particular nucleotide is sequenced) in at least 20% of the region-of-interest is less than our stringent cutoff of 300. Sensitivity for detection of low allelic frequency variants may be reduced in areas with reduced depth of coverage.

None

BACKGROUND INFORMATION: Chronic Lymphocytic Leukemia (CLL) Mutation Panel by Next Generation Sequencing
CHARACTERISTICS: Chronic lymphocytic leukemia (CLL) is a hematopoietic disorder characterized by monoclonal B-cell proliferation. Recent studies have identified recurrently mutated genes with diagnostic and/or prognostic impact in CLL and other lymphoid malignancies. The presence of certain

mutations may inform clinical management. This multigene panel by massively parallel sequencing (next generation sequencing) is a more cost-effective approach when compared to the cost of multiple single-gene tests. This test can be used to complement the morphologic and cytogenetic workup of CLL and other lymphoid malignancies.

GENES TESTED: ATM; BCL2; BIRC3*; BRAF; BTG1; BTK; CARD11; CD79B; CXCR4; DDX3X; FBXW7; IKZF3; KRAS; MAP2K1; MED12; MGA; MYD88; NOTCH1; NRAS; PLCG2; POT1; RNASEH2A; RNASEH2B; RPS15*; SAMHD1; SF3B1; TP53; XPO1; ZMYM3
*One or more exons of the preferred transcript were not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Genomic DNA was isolated from peripheral blood or bone marrow then enriched for the targeted exonic regions of the tested genes. The variant status of the targeted genes was determined by massively parallel sequencing. The hg19 (GRCh37) human genome assembly was used as a reference for identifying genetic variants. Clinically significant variants and variants of uncertain significance called in the preferred transcript are reported.

LIMITATIONS: Variants outside the targeted regions or below the limit of detection are not identified. Variants in regions that are not included in the preferred transcript for the targeted genes are not detected. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes or in repetitive or homologous regions. It is also possible some insertion/deletion variants may not be identified. Benign or likely benign variants in the preferred transcript are not reported.
The following regions were not sequenced due to technical limitations of the assay:
BIRC3 (NM_001165) exon 5
RPS15 (NM_001018) exon 3

LIMIT OF DETECTION (LOD): 5 percent variant allele fraction (VAF) for single nucleotide variants (SNV) and small variants less than 24 base pairs (bp). Variants greater than 24bp may be detected at LOD, but the analytical sensitivity may be reduced.

ANALYTICAL SENSITIVITY: The positive percent agreement (PPA) estimate for the respective variant classes (with 95 percent credibility region) are listed below. Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.
Single nucleotide variants (SNVs): 96.9 percent (95.1-98.1 percent)
Insertions/duplications (1-24bp): 98.1 percent (95.5-99.3 percent)
Insertions/duplications (greater than 24bp): greater than 99 percent (92.9-100.0 percent)
Deletions (1-24bp): 96.7 percent (92.8-98.7 percent)
Deletions (greater than 24bp): 90 percent (79.5-96.1 percent)
Multinucleotide variants (MNVs): 97 percent (93.0-99.0 percent)

CLINICAL DISCLAIMER: Results of this test must always be interpreted within the context of clinical findings and other relevant data and should not be used alone for a diagnosis of malignancy. This test is not intended to detect minimal residual disease.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

H=High, L=Low, *=Abnormal, C=Critical

EER, CLL Panel by NGS

See Note

Authorized individuals can access the ARUP Enhanced Report using the following link:

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Chronic Lymphocytic Leukemia Specimen	23-116-100739	4/26/2023 7:37:00 AM	4/26/2023 7:37:57 AM	4/26/2023 9:37:00 AM
Chronic Lymphocytic Leukemia Interp	23-116-100739	4/26/2023 7:37:00 AM	4/26/2023 7:37:57 AM	4/26/2023 9:37:00 AM
EER, CLL Panel by NGS	23-116-100739	4/26/2023 7:37:00 AM	4/26/2023 7:37:57 AM	4/26/2023 9:37:00 AM

END OF CHART

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