ARUP LABORATORIES | www.aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: (801) 583-2787, toll free: (800) 522-2787
Julio C. Delgado, MD, MS, Director of Laboratories

Client: Univ Divison Validation
50 N. Medical Drive
Salt Lake City, UT 84132
UNITED STATES

Physician: TEST,

Patient: CLL, PROD LIS3

DOB	
Gender:	Unknown
Patient Identifiers:	566220
Visit Number (FIN):	589522
Collection Date:	2/13/2020 16:55

Chronic Lymphocytic Leukemia Mutation Panel by Next Generation Sequencing (Not Orderable)

ARUP test code 3001858

Chronic Lymphocytic Leukemia Specimen	See Note
Chronic Lymphocytic Leukemia Interp	See Note

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

Result:
I. Tier 1 (Variants of known significance in myeloid malignancies):

1. NRAS c.34G>T, p.Gly12Cys (NM_002524.4)
Variant Frequency: 10.6%

Interpretation: There are two NRAS mutations detected. The RAS genes (KRAS and NRAS) encode a family of membrane-associated signal-transduction proteins involved in regulating cell growth (1, 2). Collectively, RAS mutations are found in approximately 2-7% of patients with chronic lymphocytic leukemia (CLL) (3, 4). These mutations predominantly occur at codons 12, 13, 61, 117 and 146, leading to activation of the RAS-ERK pathway (3, 5). This particular missense mutation has been reported in lymphoid malignancies (6). 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 a higher incidence of somatic trisomy 12 in patients with KRAS mutations (4). Correlation with cytogenetic findings is recommended.

2. NRAS c.181C>A, p.Gln61Lys (NM_002524.4)
Variant Frequency: 8.3%

Interpretation: This second NRAS mutation has also been reported in lymphoid malignancy (6).

II. Tier 2 (Variants of unknown significance in myeloid malignancies):

NONE DETECTED

References:
1.D. T. Bowen et al., RAS mutation in acute myeloid leukemia is associated with distinct cytogenetic subgroups but does not

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

influence outcome in patients younger than 60 years. Blood 2005. PMID: 15951308.
2.B. S. Braun, K. Shannon, Targeting Ras in myeloid leukemias. Clinical Cancer Research 2008. PMID: 18413813.
3.D. A. Landau et al., Mutations driving CLL and their evolution in progression and relapse. Nature 2015. PMID: 26466571.
4.E. Vendramini 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.
5.G. A. Hobbs, C. J. Der, RAS Mutations Are Not Created Equal. Cancer Discovery 2019. PMID: 31160330.
6.COSMIC database website: http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/
7.N. Gimenez 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.

Low coverage regions:
This list contains exons where the average sequencing depth (number of times a particular position is sequenced) for 20% or more of the region is below our stringent cutoff of 300. Sensitivity for detection of low allelic frequency mutations may be reduced in areas with low depth of coverage. The sequencing reads from these exons were manually reviewed. If high quality variants are detected in these regions, they will be listed above in Tier 1 or Tier 2.

NONE

This result has been reviewed and approved by Peng Li, M.D.

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

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 multi-gene 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, 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.
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. 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)
Multi-nucleotide 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.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement B: aruplab.com/CS

EER, CLL Panel by NGS	See Note

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Chronic Lymphocytic Leukemia Specimen	20-044-122358	2/13/2020 4:55:00 PM	2/13/2020 4:59:07 PM	2/21/2020 11:44:00 AM
Chronic Lymphocytic Leukemia Interp	20-044-122358	2/13/2020 4:55:00 PM	2/13/2020 4:59:07 PM	2/21/2020 11:44:00 AM
EER, CLL Panel by NGS	20-044-122358	2/13/2020 4:55:00 PM	2/13/2020 4:59:07 PM	2/21/2020 11:44:00 AM

END OF CHART

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