Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/17/2021
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Solid Tumor Mutation Panel, Sequencing

ARUP test code 3004294

Solid Tumor Panel By NGS Interpretation

See Note

Solid Tumor Mutation Panel NGS

Block ID: 234b
Clinical History: Adenocarcinoma
Sample Source: Ascending colon

TIER 1: Variants of Strong Clinical Significance
(variants with therapeutic, diagnostic, or prognostic
significance in the patients specific tumor type)

1. KRAS c.437C>T, p.Ala146Val (NM_004985.4)

The KRAS gene encodes a small GTPase protein involved in
regulating cell growth (11) (13). KRAS mutations are found in
approximately 30-43% of colorectal cancers (2) and activate the
MAPK and PI3K pathways. Oncogenic KRAS mutations in colorectal
cancer are associated with poor response to anti-EGFR therapy
(NCCN Clinical Practice Guidelines in Oncology: Colon and Rectal
Cancer) (9) (10). Additional clinical trials for KRAS-mutated
colorectal cancers are currently underway (clinicaltrials.gov).

TIER 2: Variants of Potential Clinical Significance
(variants with potential therapeutic, diagnostic, or prognostic
significance)

1. APC c.2623A>T, p.Lys875* (NM_000038.5)

There are two distinct APC mutations detected. The APC gene
encodes a tumor suppressor that inhibits the beta-catenin
pathway and regulates cell proliferation (1) (5). APC
inactivating mutations are found in 50-80% of sporadic colon
cancer cases (2). This particular nonsense mutation (p.Lys875*)
is presumed to inactivate APC. A recent study reports that APC
mutation status, in the context of multi-gene profiling, may
carry prognostic significance in colorectal cancer patients (12).

2. APC c.4483_4484del, p.Ser1495fs (NM_000038.5)

This is the second APC mutation. This particular frameshift
mutation (p.Ser1495fs) is also presumed to inactivate APC.

3. TP53 c.375G>A, p.Thr125Thr (NM_000546.5)

Somatic mutations in TP53 are found in 17-59% of all colorectal
cancer patients (2). This particular alteration (p.Thr125Thr) is
a synonymous variant at the last nucleotide of exon 4 which
weakens the splice donor site of intron 4 and is predicted to
cause abnormal splicing of TP53 (Alamut Visual software

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

v.2.11.0). Experimental studies have also shown this variant impairs TP53 splicing (7) (15) (14). In addition, this variant has been reported as a germline variant in hereditary cancer-predisposing syndrome and Li-Fraumeni syndrome (ClinVar VarID: 177825). This variant has been reported in a variety of cancer types, including colorectal cancer (4) (3) (6). Clinical trials for TP53-mutated colorectal cancers are currently underway (clinicaltrials.gov).

TIER 3: Variants of Unknown Clinical Significance (VUS)

None found

REFERENCES
1: Aoki K, Taketo MM, Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. J Cell Sci 2007. PMID:17881494
2: Cancer Genome Atlas Network., Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012. PMID:22810696
3: cBioPortal: http://www.cbioportal.org/
4: COSMIC: https://cancer.sanger.ac.uk/cosmic
5: Fodde R, Smits R, Clevers H, APC, signal transduction and genetic instability in colorectal cancer. Nat Rev Cancer 2001. PMID:11900252
6: ICGC: https://dcc.icgc.org/
7: Leroy B, Anderson M, Soussi T, TP53 mutations in human cancer: database reassessment and prospects for the next decade. Hum Mutat 2014. PMID:24665023
8: Li MM, Datto M, Duncavage EJ et al, Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn 2017. PMID:27993330
9: NCCN_Colon_v2_2021: NCCN Clinical Practice Guidelines in Oncology: Colon Cancer Version 2.2021 - February 9, 2021: https://www.nccn.org/professionals/physician_gls/pdf/colon_blocks.pdf
10: NCCN_Rectal_v1_2021: NCCN_Rectal_v1_2021: NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer Version 1.2021 - February 9, 2021: https://www.nccn.org/professionals/physician_gls/pdf/rectal_blocks.pdf
11: Porru M, Pompili L, Caruso C et al, Targeting KRAS in metastatic colorectal cancer: current strategies and emerging opportunities. J Exp Clin Cancer Res 2018. PMID:29534749
12: Schell MJ, Yang M, Teer JK et al, A multigene mutation classification of 468 colorectal cancers reveals a prognostic role for APC. Nat Commun 2016. PMID:27302369
13: Tan C, Du X, KRAS mutation testing in metastatic colorectal cancer. World J Gastroenterol 2012. PMID:23066310
14: Varley JM, Attwooll C, White G et al, Characterization of germline TP53 splicing mutations and their genetic and functional analysis. Oncogene 2001. PMID:11420676
15: Varley JM, Chapman P, McGown G et al, Genetic and functional studies of a germline TP53 splicing mutation in a Li-Fraumeni-like family. Oncogene 1998. PMID:9681828

This result has been reviewed and approved by [redacted]

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 allellic 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, Tier 2 or Tier 3.

None

BACKGROUND INFORMATION: Solid Tumor Mutation Panel by Next Generation Sequencing

CHARACTERISTICS: Specific somatic variants have been discovered in multiple cancer-related genes and have diagnostic, therapeutic and/or prognostic utility in several cancer types. Targeted next generation sequencing is utilized in this test for the detection of hotspot variants within 44 cancer-related genes and includes extended RAS variant detection. The personalized variant profile may be useful for prediction of patient diagnosis, prognosis and/or response to targeted therapies in solid tumors including, melanoma, gastrointestinal stromal tumors (GIST), colorectal cancers, bladder cancers, and hepatocellular cancers.

GENES TESTED: AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CTNNB1, DDR2, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KDR, KIT, KRAS, MAP2K1, MET, MTOR, NOTCH1, NRAS, NTRK1, PDGFRA, PIK3CA, PTEN, RB1, RET, ROS1, SMAD4, SMO, STK11, TERT promoter, TP53, VHL. A full list of targeted regions within the above genes is available through this link: http://ltd.aruplab.com/Tests/Pdf/375.

METHODOLOGY: Genomic DNA is isolated from microscopically-guided dissection of tumor tissue and then enriched for the targeted regions of the tested genes. The variant status of the 44 targeted genes is determined by massively parallel sequencing (next generation sequencing). The hg19 (GRCh37) reference sequence is used as a reference for identifying genetic variants.

LIMITATIONS: This test will not detect variants in areas outside the targeted genomic regions or below the limit of detection. Copy number alterations, translocations, microsatellite instability, and tumor mutational burden will not be detected. If clinical indication is lung cancer, additional clinical evaluation may be considered for complete genetic analysis including, detection of translocations or gene rearrangements. This test is not intended to detect minimal residual disease. This test evaluates for variants in tumor tissue only and cannot distinguish between somatic and germline variants. Therefore, if a hereditary/familial cancer is of clinical concern, consider additional clinical evaluation and genetic counseling prior to additional testing. In some cases, variants may not be identified due to technical limitations in the presence of known pseudogenes, homologous regions and/or low mapability regions. This includes variants in PTEN exons 1, 2, 4, 5, 6, 7, 8 and 9; MAP2K1 exons 2, 7 and 11; CDKN2A exon 2, PIK3CA exons 10 and 14; GNAQ exon 5; EZH2 exon 18; and BRAF exon 11. It is also possible that some large insertion/deletion variants (especially those greater than 60bp) may not be detected. Tissue samples yielding at least 10ng are acceptable but may yield suboptimal results if yield is less than 50ng.

LIMIT OF DETECTION: 5 percent mutant allele for single nucleotide variants (SNV), small to medium sized multi-nucleotide variants (MNV) (less than 60bp).

ANALYTICAL SENSITIVITY (PPA): Analytical sensitivity for all variant classes available through this link: http://ltd.aruplab.com/Tests/Pdf/375.

CLINICAL DISCLAIMER: Results of this test must always be interpreted within the clinical context 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 US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

EER Solid Tumor Panel NGS	EERUnavailable Corrected Corrected from See Note on 01/06/22 14:25:07 MST by 23116.
Solid Tumor Panel by NGS Block ID	123

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Solid Tumor Panel By NGS Interpretation	21-323-115899	11/19/2021 3:36:00 PM	11/19/2021 3:36:34 PM	11/19/2021 3:44:00 PM
EER Solid Tumor Panel NGS	21-323-115899	11/19/2021 3:36:00 PM	11/19/2021 3:36:34 PM	1/6/2022 2:25:00 PM
Solid Tumor Panel by NGS Block ID	21-323-115899	11/19/2021 3:36:00 PM	11/19/2021 3:36:34 PM	11/19/2021 3:41 00 PM

END OF CHART

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