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

Physician: Doctor, Example

Patient: Patient, Example

DOB	10/9/1990
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Li-Fraumeni (TP53) Sequencing and Deletion/Duplication

ARUP test code 2009313

Li-Fraumeni (TP53) Seq, DelDup Spcm	See Note

Li-Fraumeni (TP53) Seq, DelDup Interp	Positive

TEST PERFORMED - 2009313
TEST DESCRIPTION - Li-Fraumeni (TP53) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the TP53 gene.

DNA VARIANT
Classification: Pathogenic
Gene: TP53
Nucleic Acid Change: c.916C>T; Heterozygous
Amino Acid Alteration: p.Arg306Ter

INTERPRETATION
According to information provided to ARUP, this individual has a history of hematologic malignancy (acute lymphocytic leukemia). One copy of a pathogenic variant, c.916C>T; p.Arg306Ter, was detected in the TP53 gene by Sanger sequencing in the submitted blood sample. No TP53 variants were detected by deletion/duplication analysis. The identified variant may represent either a constitutional (i.e., germline) or somatic variant. Targeted testing for the identified variant in a different sample type, unaffected by malignancy, may help determine if the detected variant is constitutional. If constitutional, then this result would be consistent with a diagnosis of Li-Fraumeni syndrome (LFS), a hereditary cancer predisposition syndrome associated with early-onset and multiple primary malignancies. Clinical manifestations of LFS are variable. This individual's offspring would have a 50 percent chance of inheriting a causative germline variant.

Additionally, as this assay may not detect low-level somatic TP53 variants related to malignancy, this result does not exclude the presence of additional TP53 variants. Interpretation of this test result may also be impacted if the patient had an allogeneic stem cell transplantation.

Evidence for variant classification: The TP53 c.916C>T; p.Arg306Ter variant (rs121913344) is published in the medical literature in several individuals with cancer or suspected Li-Fraumeni syndrome, and is described as segregating with disease (Hettmer 2014, Holmfeldt 2013, Klein 2017, Paixao 2018, Rajkumar 2018). The variant is reported as pathogenic or likely pathogenic in the ClinVar database (Variation ID: 142144) but is

absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Considering available information, this variant is classified as pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Targeted sequencing for the identified variant in a different sample type, unaffected by malignancy, may be helpful to assess if the identified variant is constitutional versus somatic in origin (Familial Mutation, Targeted Sequencing; ARUP test code 2001961). If the identified variant is confirmed to be constitutional, at-risk family members should be offered targeted testing as well. If the indication for testing is to evaluate TP53 variants for diagnostic, prognostic, and/or therapeutic significance related to this individual's hematologic malignancy, consideration should be given to ordering an assay that is designed to detect somatic TP53 variants.

COMMENTS
Reference Sequence: GenBank # NM_ 000546.5 (TP53)
Nucleotide numbering begins at the "A" of the ATG initiation codon
Likely benign and benign variants are not reported.

REFERENCES
Hettmer S et al. Anaplastic rhabdomyosarcoma in TP53 germline mutation carriers. Cancer. 2014 Apr 1;120(7):1068-75.

Holmfeldt L et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet. 2013 Mar;45(3):242-52.

Klein JD and Kupferman ME. Li-Fraumeni syndrome presenting as mucosal melanoma: Case report and treatment considerations. Head Neck. 2017 Feb;39(2):E20-E22.

Paixao D et al. Whole-body magnetic resonance imaging of Li-Fraumeni syndrome patients: observations from a two rounds screening of Brazilian patients. Cancer Imaging. 2018 Aug 14;18(1):27.

Rajkumar T et al. Targeted Resequencing of 30 Genes Improves the Detection of Deleterious Mutations in South Indian Women with Breast and/or Ovarian Cancers. Asian Pac J Cancer Prev. 2015;16(13):5211-7.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Li-Fraumeni (TP53) Sequencing and Deletion/Duplication
CHARACTERISTICS: Predisposition for developing early-onset and multiple primary cancers, particularly soft tissue and bone sarcomas, adrenocortical carcinoma, brain tumors, premenopausal breast cancer, and other malignancies.
PREFALENCE: 1 in 5,000 - 1 in 20,000.
INHERITANCE: Autosomal dominant.
PENETRANCE: Approximately 50 percent by age 30 years and 90 percent by age 60 years.
CAUSE: Pathogenic germline mutations in the TP53 gene.
CLINICAL SENSITIVITY: 80 percent for individuals meeting classic Li-Fraumeni syndrome (LFS) criteria.
METHODOLGY: Bidirectional sequencing of all coding regions and intron-exon boundaries of the TP53 gene; Multiplex Ligation-dependent Probe Amplification (MLPA) to detect large TP53 deletions/duplications.
ANALYTICAL SENSITIVITY AND SPECIFICITY: Greater than 95 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations and deep intronic mutations will not be detected. Deletion/duplication breakpoints will not be determined. This assay is not designed to detect somatic variants associated with malignancy. Interpretation of this test result may be impacted if the patient has had an allogeneic stem cell transplantation.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online at www.aruplab.com.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Li-Fraumeni (TP53) Seq, DelDup Spcm	19-310-402424	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Li-Fraumeni (TP53) Seq, DelDup Interp	19-310-402424	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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