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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 2013449

Gastrointestinal Cancer Panel - Spcmn: Whole Blood

Gastrointestinal Cancer Panel - Interp: **Positive** *

RESULT
One pathogenic variant was detected in the TP53 gene.

PATHOGENIC VARIANT
Gene: TP53 (NM_000546.6)
Nucleic Acid Change: c.743G>A; Heterozygous
Amino Acid Alteration: p.Arg248Gln
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.743G>A; p.Arg248Gln, was detected in the TP53 gene by massively parallel sequencing. Pathogenic germline variants in TP53 are associated with autosomal dominant Li-Fraumeni syndrome (MIM: 151623), as well as with increased risk for a variety of cancers, including breast (MIM: 114480), brain (MIM: 137800), liver (MIM: 114550), bone (MIM: 259500), colorectal (MIM: 114500), nasopharyngeal (MIM: 607107), and pancreatic cancers (MIM: 260350). This result is consistent with a diagnosis of Li-Fraumeni syndrome; clinical manifestations are variable. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology and limitations of this test.

Evidence for variant classification:
The TP53 c.743G>A; p.Arg248Gln variant (rs11540652) is reported in the germline of several individuals and families with Li-Fraumeni syndrome and TP53-associated cancers (see Grill 2021, Masciari 2011, Villani 2011, Wu 2011). This variant has occurred de novo (Behjati 2014, Bendig 2004, Toguchida 1992), and at least one case of germline mosaicism has been reported (Behjati 2014). Functional analyses have shown that the variant protein has reduced transcriptional activity and altered function (Barakat 2011, Grill 2021, Monti 2007). This variant is reported in ClinVar (Variation ID: 12356), and classified as pathogenic by an expert panel (Fortuno 2021). This variant is only observed on three alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 248 is highly conserved, located in a hotspot, and computational analyses predict that this variant is deleterious (REVEL: 0.934). Based on available information, this variant is considered to be pathogenic.

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

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic TP53 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Barakat K et al. Effects of temperature on the p53-DNA binding interactions and their dynamical behavior: comparing the wild type to the R248Q mutant. PLoS One. 2011;6(11):e27651. PMID: 22110706.
Behjati S et al. A pathogenic mosaic TP53 mutation in two germ layers detected by next generation sequencing. PLoS One. 2014 May 8;9(5):e96531. PMID: 24810334.
Bendig I et al. Identification of novel TP53 mutations in familial and sporadic cancer cases of German and Swiss origin. Cancer Genet Cytogenet. 2004 Oct 1;154(1):22-6. PMID: 15381368.
Fortuno C et al. ClinGen TP53 Variant Curation Expert Panel. Specifications of the ACMG/AMP variant interpretation guidelines for germline TP53 variants. Hum Mutat. 2021 Mar;42(3):223-236. PMID: 33300245.
Grill S et al. TP53 germline mutations in the context of families with hereditary breast and ovarian cancer: a clinical challenge. Arch Gynecol Obstet. 2021 Jun;303(6):1557-1567. PMID: 33245408.
Masciari S et al. Gastric cancer in individuals with Li-Fraumeni syndrome. Genet Med. 2011 Jul;13(7):651-7. PMID: 21552135.
Monti P et al. Transcriptional functionality of germ line p53 mutants influences cancer phenotype. Clin Cancer Res. 2007 Jul 1;13(13):3789-95. PMID: 17606709.
Toguchida J et al. Prevalence and spectrum of germline mutations of the p53 gene among patients with sarcoma. N Engl J Med. 1992 May 14;326(20):1301-8. PMID: 1565143.
Villani A et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol. 2011 Jun;12(6):559-67. PMID: 21601526.
Wu CC et al. Joint effects of germ-line TP53 mutation, MDM2 SNP309, and gender on cancer risk in family studies of Li-Fraumeni syndrome. Hum Genet. 2011 Jun;129(6):663-73. PMID: 21305319.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/ Duplication
CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary gastrointestinal (GI) cancer. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50) and multiple, multifocal, and/or similar cancers in a single individual or in closely related family member(s). Pathogenic variants in the genes analyzed by this panel cause variable phenotypes and cancer risks, including non-GI cancers. Lynch syndrome (LS), the most common hereditary predisposition to colorectal cancer, is caused by pathogenic variants in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes.

EPIDEMIOLOGY: Greater than 2-4 percent of colorectal cancers are associated with a hereditary cause. Prevalence of LS in the general population has been estimated at 1 in 279 individuals.

CAUSE: Pathogenic germline variants in genes associated with hereditary GI cancer

INHERITANCE: Autosomal dominant, except for: SDHD, which is autosomal dominant with parent-of-origin effect; MLH3, MSH3, and NTHL1, which are autosomal recessive; and MUTYH, which is autosomal recessive but may also have autosomal dominant risks that are not well-defined. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

GENES TESTED: APC*; AXIN2; BMPR1A*; CDH1*; CHEK2*; EPCAM**; KIT; MLH1; MLH3*; MSH2; MSH3; MSH6; MUTYH; NTHL1; PDGFRA*; PMS2; POLD1; POLE; PTEN*; SDHA*; SDHB; SDHC*; SDHD*; SMAD4; STK11; TP53

* - One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

** - Deletion/duplication analysis of EPCAM (NM_002354) exon 9 only, sequencing is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes (including selected PTEN promoter variants), followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis. Testing of selected exons (and exon/intron boundaries) of PMS2, PTEN and MSH2 was performed by bidirectional Sanger sequencing. Deletion/duplication testing of PMS2 was performed by multiplex ligation-dependent probe amplification (MLPA).

ANALYTICAL SENSITIVITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes. The analytical sensitivity for MLPA is greater than 99 percent.

LIMITATIONS: A negative result does not exclude a heritable form of cancer. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
APC (NM_001354896) exon 12
APC (NM_001354898, NM_001354904) exon 2
APC (NM_001354900) exon 11
CHEK2 (NM_001005735) exon 3
CHEK2 (NM_001349956) exon 4
PDGFRA (NM_001347827) exon 17
PDGFRA (NM_001347828) exon 2
PDGFRA (NM_001347830) exon 1
SDHA (NM_004168) exon 14
SDHA (NM_001294332) exon 13
SDHA (NM_001330758) exon 12
SDHC (NM_001035511) partial exon 5 (Chr1:161332225-161332330)
SDHC (NM_001278172) partial exon 4 (Chr1:161332225-161332330)
SDHD (NM_001276506) exon 4

Deletions/duplications will not be called for the following exons:
APC (NM_001354896) 12; APC (NM_001354898, NM_001354904) 2; APC (NM_001354900) 11; BMPR1A (NM_004329) 12-13; CDH1 (NM_001317185) 10; CHEK2 (NM_007194) 11-15; CHEK2 (NM_001005735) 3,12-16; CHEK2 (NM_001257387) 12-16; CHEK2 (NM_001349956) 4,10-14; CHEK2 (NM_145862) 10-14; MLH3 (NM_001040108) 7-8; MLH3 (NM_014381) 7; PDGFRA (NM_001347827) 17; PDGFRA (NM_001347828) 2; PDGFRA (NM_001347830) 1; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10; SDHA (NM_004168) 1,10-15; SDHA (NM_001294332) 1,9-14; SDHA (NM_001330758) 1,10-13; SDHD (NM_001276506) 4

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.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Gastrointestinal Cancer Panel - Spcmn	22-301-104949	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Gastrointestinal Cancer Panel - Interp	22-301-104949	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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