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

Physician: Doctor, Example

Patient: Patient, Example

DOB	9/13/1990
Gender:	Male
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 MSH6 gene.

PATHOGENIC VARIANT
Gene: MSH6 (NM_000179.3)
Nucleic Acid Change: c.3939_3957dup; Heterozygous
Amino Acid Alteration: p.Ala1320SerfsTer5
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.3939_3957dup; p.Ala1320SerfsTer5, was detected in the MSH6 gene by massively parallel sequencing. This result is consistent with a diagnosis of Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC), a hereditary cancer predisposition syndrome. A single pathogenic MSH6 variant increases the risk for colorectal, uterine, and other cancers; lifetime risks for different cancers vary. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals. Other genetic/environmental factors may influence an individual's risk of developing cancer. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

In addition, autosomal recessive inheritance of two MSH6 pathogenic variants is associated with constitutional mismatch repair-deficiency (CMMRD), a childhood cancer predisposition syndrome characterized by hematologic, brain, and intestinal tumors (Wimmer 2014, MIM: 276300); thus, this individual is at least a carrier of this disorder.

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 MSH6 c.3939_3957dup; p.Ala1320SerfsTer5 variant (rs63750767), has been described in the literature in multiple individuals with Lynch syndrome (Carter 2018, Chong 2009, Goodfellow 2003, Kerr 2016). This variant is also reported in ClinVar (Variation ID: 89486). This variant is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant creates a frameshift by duplicating 19 nucleotides, so is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay.

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

Based on available information, this variant is considered pathogenic.

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 MSH6 variant (Familial Targeted Sequencing, ARUP test code 3005867). Counseling for potential reproductive risk associated with CMMRD is recommended (NCCN Guidelines).

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
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (2.2023). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
Carter NJ et al. Germline pathogenic variants identified in women with ovarian tumors. Gynecol Oncol. 2018 Dec;151(3):481-488. PMID: 30322717.
Chong G et al. High frequency of exon deletions and putative founder effects in French Canadian Lynch syndrome families. Hum Mutat. 2009; 30(8):E797-812.
Goodfellow PJ et al. Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers. Proc Natl Acad Sci U S A. 2003; 100(10):5908-13.
Kerr L et al. A cohort analysis of men with a family history of BRCA1/2 and Lynch mutations for prostate cancer. BMC Cancer. 2016 Jul 25;16:529. PMID: 27456091.
Wimmer K et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). Med Genet. 2014 Jun;51(6):355-65. PMID: 24737826.

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	24-116-401196	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Gastrointestinal Cancer Panel - Interp	24-116-401196	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