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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/6/1950
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** *

INDICATION FOR TESTING
Personal diagnosis of colon cancer.

RESULT
One pathogenic variant was detected in the MSH6 gene.

PATHOGENIC VARIANT
Gene: MSH6 (NM_000179.3)
Nucleic Acid Change: c.2150_2153delTCAG Heterozygous
Amino Acid Alteration: p.Val717AlafsTer18
Inheritance: Autosomal dominant

INTERPRETATION
One copy of a pathogenic variant, c.2150_2153delTCAG; p.Val717AlafsTer18, was detected in the MSH6 gene by massively parallel sequencing. This result is consistent with a diagnosis of Lynch / hereditary non-polyposis colorectal cancer (HNPCC) syndrome (MIM: 614350), an autosomal dominant hereditary cancer syndrome. Other genetic and/or environmental factors may influence severity of clinical phenotype. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals. Offspring of this individual have a 50 percent chance of inheriting the variant.

In addition, autosomal recessive inheritance of two MSH6 pathogenic variants is associated with mismatch repair cancer syndrome-3 a condition characterized by brain tumors hematologic malignancy, and gastrointestinal tumors (MIM: 619097). Thus, this individual is at least a carrier of this disorder.

No additional pathogenic variants were identified in the other targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test. No sequence variants and large exonic deletions or duplications were detected in PMS2 by Sanger sequencing and by multiplex ligation dependent probe amplification (MLPA).

Evidence for variant classification:
The MSH6 c.2150_2153delTCAG; p.Val717AlafsTer18 variant (rs267608058), also known as c.2147_2150delCAGT or 2149delTCAG, is reported in the literature in multiple individuals affected with Lynch syndrome and associated cancers (Baglietto 2010,

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

DeRycke 2017, Hirasawa 2017, Kolodner 1999, Nilbert 2009, Pal 2012, Sun 2017, Talseth-Palmer 2010, Walsh 2011). This variant is also reported in ClinVar (Variation ID: 89256). It is only observed on two alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant causes a frameshift by deleting 4 nucleotides, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Additionally, several downstream truncating variants have been described in individuals with various cancers and are considered pathogenic (Nilbert 2009, Pal 2012). Based on available information, this variant is considered to be 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 Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not reported.
Variants in the following regions may not be detected by NGS with sufficient confidence in this sample due to technical limitations; reportable variants are confirmed by Sanger sequencing:
NONE

REFERENCES
Baglietto L et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst. 2010 Feb 3;102(3):193-201. PMID: 20028993

DeRycke MS et al. Targeted sequencing of 36 known or putative colorectal cancer susceptibility genes. Mol Genet Genomic Med. 2017 Jul 23;5(5):553-569. PMID: 28944238

Hirasawa A et al. Prevalence of pathogenic germline variants detected by multigene sequencing in unselected Japanese patients with ovarian cancer. Oncotarget. 2017 Nov 28;8(68):112258-112267. PMID: 29348823

Kolodner RD et al. Germ-line msh6 mutations in colorectal cancer families. Cancer Res. 1999 Oct 15;59(20):5068-74. PMID: 10537275

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal: https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

Nilbert M et al. Major contribution from recurrent alterations and MSH6 mutations in the Danish Lynch syndrome population. Fam Cancer. 2009;8(1):75-83. PMID: 18566915

Pal T et al. Frequency of mutations in mismatch repair genes in a population-based study of women with ovarian cancer. Br J Cancer. 2012 Nov 6;107(10):1783-90. PMID: 23047549

Sun J et al. Germline Mutations in Cancer Susceptibility Genes in a Large Series of Unselected Breast Cancer Patients. Clin Cancer Res. 2017 Oct 15;23(20):6113-6119. PMID: 28724667

Talseth-Palmer BA et al. MSH6 and PMS2 mutation positive Australian Lynch syndrome families: novel mutations, cancer risk and age of diagnosis of colorectal cancer. Hered Cancer Clin Pract. 2010 May 21;8(1):5. PMID: 20487569

Walsh T et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011 Nov 1;108(44):18032-7. PMID: 22006311

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This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/ Duplication

CHARACTERISTICS: Pathogenic variants in multiple genes have been implicated in hereditary gastrointestinal (GI) cancer. Germline variants in genes associated with hereditary GI cancer may also confer risk for other non-GI cancers. Common signs of a hereditary GI cancer syndrome include a GI cancer diagnosed at a young age (less than 50 years old), multiple and/or rare tumors in a single individual, and a family history of the same or related types of cancer. Lynch syndrome is caused by pathogenic variants in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes. Individuals with Lynch syndrome are at an increased risk for colorectal, endometrial, stomach, ovarian, and other cancers.

EPIDEMIOLOGY: Approximately 300,000 new cases of cancer within the digestive organs are diagnosed in the U.S. per year. Prevalence of Lynch syndrome in the general population has been estimated at 1 in 440 individuals.

CAUSE: At least 2-4 percent of colorectal cancers are associated with a hereditary cause.

INHERITANCE: Autosomal dominant, with the exception of the SDHD gene which is autosomal dominant with parent-of-origin effect, and the MUTYH gene 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.

PENETRANCE: Varies, depending on the gene and specific variant.

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

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
** - Deletion/duplication detection is not available for this gene.
**** - Deletion/duplication only; sequencing is not available for this gene.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, including the PTEN promoter region, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis. Analysis of the PMS2 gene was performed by bidirectional Sanger sequencing of coding regions and their respective exon intron boundaries as well as multiplex ligation-dependent probe amplification (MLPA). Targeted sequencing was performed for the CHEK2 c.1100delC variant.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

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. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. 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:
CHEK2(NM_001349956) exon(s) 4
CHEK2(NM_001005735) exon(s) 3
CHEK2(NM_007194) exon(s) 10,12,13,14,15
SDHC(NM_001035511) exon(s) 5
SDHD(NM_001276506) exon(s) 4

Single exon deletions/duplications will not be called for the following exons:
APC(NM_001127511) 1;BMPR1A(NM_004329) 9;CDH1(NM_004360) 1;CHEK2(NM_001005735) 3;CHEK2(NM_007194) 11,12,14,15;MSH2(NM_000251) 1;MSH2(NM_001258281) 2;MSH6(NM_000179) 10;MUTYH(NM_001128425) 1;NTHL1(NM_002528) 3,4,5,6;POLD1(NM_002691) 6,18,25;PTEN(NM_000314) 8,9;PTEN(NM_001304717) 1;SDHD(NM_001276506) 4;TP53(NM_001126113) 10;TP53(NM_001126114) 10

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	22-063-401108	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Gastrointestinal Cancer Panel - Interp	22-063-401108	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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