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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	12/31/1752
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

HNPCC/Lynch Syndrome (MSH6) Sequencing and Deletion/Duplication

ARUP test code 0051656

MSH6 FGA Specimen	Whole Blood	
Lynch Syndrome (MSH6) Interpretation	**Positive**	*

H – high L – low * – abnormal C – critical

TEST PERFORMED - 0051656
TEST DESCRIPTION - HNPCC/Lynch Syndrome (MSH6) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Not Provided

RESULT
One pathogenic variant was detected in the MSH6 gene.

DNA VARIANT(S)
Classification: Pathogenic
Gene: MSH6
Nucleic Acid Change: c.1190_1191delAT; Heterozygous
Amino Acid Alteration: p.Tyr397fs
Also Known As:

INTERPRETATION
One pathogenic variant, c.1190_1191delAT, p.Tyr397fs, was detected in the MSH6 gene by sequencing. No pathogenic MSH6 variants were detected by deletion/duplication analysis. This result is consistent with a diagnosis of Lynch syndrome/HNPCC. This individual's offspring have a 50 percent chance of inheriting the causative variant.

Evidence for variant classification(s): The MSH6 c.1190_1191delAT, p.Tyr397fs variant (rs63750439) has been reported in multiple individuals with colon cancer showing high microsatellite instability and absence of MSH6 protein by immunohistochemistry (Plaschke 2001, Steinke 2008, You 2010). It is listed as pathogenic in ClinVar (Variation ID: 89178), and observed twice in the Genome Aggregation Database general population database (2/245974 alleles). The variant introduces a frameshift, and is predicted to result in a truncated protein or an absent transcript. Based on the above information, the p.Tyr397fs variant is classified as pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Targeted sequencing for the identified variant is recommended for at-risk adult family members (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_000179.2 (MSH6)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Benign variants are not included in this report but are available upon request.

REFERENCES

This result has been reviewed and approved by Rong Mao, M.D.

BACKGROUND INFORMATION: HNPCC/Lynch Syndrome (MSH6)
Sequencing and Deletion/Duplication

CHARACTERISTICS: Increased risk of colorectal and extra-colonic cancers including endometrial, renal pelvis, ureter, ovary, stomach, small intestine and hepatobiliary tract.
INCIDENCE: 1-2 percent of colorectal cancer is due to mismatch repair gene mutations.
INHERITANCE: Autosomal dominant.
PENETRANCE OF MSH6 MUTATIONS: Risk of colorectal cancer is 40 percent in men and 20 percent in women up to age 80. Women also have a 40 percent risk for endometiral cancer up to age 80.
CAUSE: Pathogenic germline MLH1, MSH2, MSH6, and PMS2 gene mutations.
GENE TESTED: MSH6
CLINICAL SENSITIVITY: Approximately 5 percent of Lynch syndrome is due to MSH6 mutations.
METHODOLOGY: Bidirectional sequencing of MSH6 coding regions and intron-exon boundaries; multiplex ligation-dependent probe amplification (MLPA) to detect large MSH6 exonic deletions.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
TEST LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. The breakpoints of large deletions/duplications will not be determined. Regulatory region, deep intronic mutations and mutations in genes other than MSH6 will not be detected.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
MSH6 FGA Specimen	17-317-106849	11/13/2017 11:50:00 AM	11/13/2017 11:56:31 AM	11/13/2017 2:16:18 PM
Lynch Syndrome (MSH6) Interpretation	17-317-106849	11/13/2017 11:50:00 AM	11/13/2017 11:56:31 AM	11/13/2017 2:16:18 PM

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