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

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/17/1967
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

HNPCC/Lynch Syndrome (PMS2) Sequencing and Deletion/Duplication

ARUP test code 0051737

PMS2 FGA Specimen	Whole Blood

Lynch Syndrome (PMS2) Interpretation

Positive *

TEST PERFORMED - 0051737
TEST DESCRIPTION - HNPCC/Lynch Syndrome (PMS2) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic deletion was detected in the PMS2 gene.

DNA VARIANT
Classification: Pathogenic
Gene: PMS2
Nucleic Acid Change: deletion of exons 7-14 Heterozygous

INTERPRETATION
One copy of a pathogenic variant, deletion of exons 7-14, was detected in the PMS2 gene by deletion/duplication analysis. No pathogenic variants were detected by 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 PMS2 variant increases the risk for colorectal, uterine, and other cancers; lifetime risks for different cancers vary. In addition, other genetic and/or environmental factors may influence the clinical phenotype. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals. This individual's offspring have a 50 percent chance of inheriting the causative pathogenic variant.

In addition, autosomal recessive inheritance of two PMS2 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.

Evidence for variant classification: The deletion of PMS2 exons 7-14 is reported in the literature in an individual with constitutional mismatch repair deficiency who carried a second large PMS2 deletion on the opposite chromosome (Lindsay 2013). It is also reported in the ClinVar database (Variation ID: 455090). This is an in-frame deletion, leaving the remainder of the protein in-frame. Based on available information, the deletion of exons 7-14 in PMS2 is considered to be pathogenic.

RECOMMENDATIONS

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

Genetic consultation is indicated, including a discussion of medical screening and management. Testing for the identified variant is recommended for at-risk adult family members (HNPCC/Lynch Syndrome Deletion/Duplication, ARUP test code 2001728).

COMMENTS
Reference Sequence: GenBank # NM_000535.5 (PMS2)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Lindsay H et al. Simultaneous colonic adenocarcinoma and medulloblastoma in a 12-year-old with biallelic deletions in PMS2. J Pediatr. 2013 Aug;163(2):601-3.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (1.2020). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. (Accessed January 2021).

Wimmer K, Kratz CP, Vasen HF, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 2014;51:355-365.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: HNPCC/Lynch Syndrome (PMS2) 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: Unknown for PMS2 mutations
CAUSE: Pathogenic germline MLH1, MSH2, MSH6, and PMS2 gene mutations.
GENE TESTED: PMS2
CLINICAL SENSITIVITY: Less than 5 percent of Lynch syndrome cases are due to PMS2 mutations.
METHODOLOGY: Bidirectional sequencing of PMS2 coding regions and intron-exon boundaries; multiplex ligation-dependent probe amplification (MLPA) to detect large PMS2 exonic deletions.
ANALYTICAL SENSITIVITY & SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations and deep intronic mutations will not be detected. Mutations in genes other than PMS2 are not evaluated. 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.

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

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
PMS2 FGA Specimen	20-359-122482	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Lynch Syndrome (PMS2) Interpretation	20-359-122482	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