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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	2/26/1945
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Lynch Syndrome Panel, Sequencing and Deletion/Duplication

ARUP test code 3001605

LS Specimen	Whole Blood

LS Interp

Positive

RESULT
One pathogenic variant was detected in the PMS2 gene.

PATHOGENIC VARIANT
Gene: PMS2 (NM_000535.7)
Nucleic Acid Change: c.986C>G; Heterozygous
Amino Acid Alteration: p.Ser329Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.986C>G; p.Ser329Ter, was detected in the PMS2 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 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 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.

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

Evidence for variant classification:
The PMS2 c.986C>G; p.Ser329Ter variant (rs1461669945), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 545975). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. 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 PMS2 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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 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 (2.2022). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
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: Lynch Syndrome Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is a hereditary cancer syndrome that predisposes individuals to colorectal, endometrial, ovarian, stomach, small bowel, and other cancers. LS is the most common hereditary colorectal cancer (CRC) syndrome.

EPIDEMIOLOGY: LS affects approximately 1 in 279 individuals in the general population. Approximately 2-4 percent of CRC cases are associated with LS.

CAUSE: LS results from heterozygous germline pathogenic variants in the DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, and PMS2. In addition, exon 9 deletions of the EPCAM gene lead to MSH2 inactivation, and thus results in LS.

INHERITANCE: Autosomal dominant.

PENETRANCE: Varies, depending on the gene.

CLINICAL SENSITIVITY: Varies, depending on the gene.

GENES TESTED: MLH1, MSH2, MSH6, PMS2, EPCAM*
*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, 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. Human genome build 19 (Hg 19) was used for data analysis. Testing of selected exons (and exon/intron boundaries) of PMS2 and MSH2 was performed by bidirectional Sanger sequencing. Multiplex ligation-dependent probe amplification (MLPA) of the targeted genes, including the MHS2 10Mb inversion of exons 1-7.

ANALYTICAL SENSITIVITY/SPECIFICITY: 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. 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 diagnosis of LS. 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. 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. Noncoding transcripts were not analyzed.

Single exon deletions/duplications may not be called for the following exons:
MLH1 (NM_000249) 12

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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
LS Specimen	23-101-402350	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
LS Interp	23-101-402350	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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