

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

Physician: Doctor, Example

**Patient: Patient, Example**

**DOB:** 1/10/1974  
**Sex:** Male  
**Patient Identifiers:** 01234567890ABCD, 012345  
**Visit Number (FIN):** 01234567890ABCD  
**Collection Date:** 01/01/2017 12:34

**Lynch Syndrome Panel, Sequencing and Deletion/Duplication**

ARUP test code 3001605

LS Specimen	whole Blood
LS Interp	<p><b>Positive</b></p> <p><b>RESULT</b> One pathogenic variant was detected in the PMS2 gene.</p> <p><b>PATHOGENIC VARIANT</b> Gene: PMS2 (NM_000535.5) Nucleic Acid Change: c.736_741delinsTGTGTGTAAG; Heterozygous Amino Acid Alteration: p.Pro246CysfsTer3 Inheritance: Autosomal dominant</p> <p><b>INTERPRETATION</b> One pathogenic variant, c.736_741delinsTGTGTGTAAG; p.Pro246CysfsTer3, 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.</p> <p>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; OMIM (R)); thus, this individual is at least a carrier of this disorder.</p> <p>Please refer to the background information included in this report for a list of the genes analyzed, methodology used, and limitations of this test.</p> <p><b>Evidence for variant classification:</b> The PMS2 c.736_741delinsTGTGTGTAAG; p.Pro246CysfsTer3 variant (rs267608150, ClinVar Variation ID: 91366) is reported in the literature in multiple individuals affected with Lynch syndrome or associated cancers (Buchanan 2014, Clendenning 2008) and is also reported in trans to a pathogenic PMS2 variant in an individual with constitution mismatch repair deficiency (Herkert 2011). This variant is absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant causes a frameshift by deleting 6 and inserting 11 nucleotides, so it is predicted to result in a truncated protein</p>

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

Unless otherwise indicated, testing performed at:

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Jonathan R. Genzen, MD, PhD, Laboratory Director

Patient: Patient, Example  
ARUP Accession: 25-077-108883  
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Page 1 of 4 | Printed: 5/5/2025 11:27:53 AM

or mRNA subject to nonsense-mediated decay. 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 PMS2 variant (Familial Targeted Sequencing, ARUP test code 3005867). Counseling for potential reproductive risk associated with CMMRD syndrome is recommended (NCCN Guidelines).

#### 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

Buchanan DD et al. Tumor mismatch repair immunohistochemistry and DNA MLH1 methylation testing of patients with endometrial cancer diagnosed at age younger than 60 years optimizes triage for population-level germline mismatch repair gene mutation testing. J Clin Oncol. 2014;32(2):90-100. PMID: 24323032.  
Clendenning M et al. A frame-shift mutation of PMS2 is a widespread cause of Lynch syndrome. J Med Genet. 2008 45(6):340-5. PMID: 18178629.  
Herkert JC et al. Paediatric intestinal cancer and polyposis due to bi-allelic PMS2 mutations: case series, review and follow-up guidelines. Eur J Cancer. 2011;47(7):965-982. PMID: 21376568.  
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (3.2024):  
[https://www.nccn.org/professionals/physician\\_gls/pdf/genetics\\_ceg.pdf](https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf)  
OMIM(R) Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.  
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\*

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Page 2 of 4 | Printed: 5/5/2025 11:27:53 AM

\*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 MSH2 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	25-077-108883	3/18/2025 9:43:00 AM	3/19/2025 11:49:55 AM	4/1/2025 2:00:00 PM
LS Interp	25-077-108883	3/18/2025 9:43:00 AM	3/19/2025 11:49:55 AM	4/1/2025 2:00:00 PM

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Page 3 of 4 | Printed: 5/5/2025 11:27:53 AM

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END OF CHART

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Page 4 of 4 | Printed: 5/5/2025 11:27:53 AM