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Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108-
USA

Provider: 68912 -arup,arup

Patient: **Cert, LS NGS 2**
DOB:
Sex: Male
Patient Identifiers: 33962
Visit Number (FIN): 34270
Client Supplied ID:

Specimen Collected: 24-Jan-22 09:12

Lynch Syndrome Panel by NGS, DelDup | **Received: 24-Jan-22 09:18** **Report/Verified: 24-Jan-22 09:23**

Procedure	Result	Units	Reference Interval
Lynch Syndrome Specimen	See Note		
LS Interp	Positive [f1 i1]		

Result Footnote

f1: LS Interp

RESULT
One pathogenic variant was detected in the MSH2 gene.

PATHOGENIC VARIANT
Gene: MSH2 (NM_000251.1)
Nucleic Acid Change: c.2113delG; Heterozygous
Amino Acid Alteration: p.Val705TrpfsTer5
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.2113delG; p.Val705TrpfsTer5, was detected in the MSH2 gene by massively parallel sequencing. This result is consistent with a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC), a hereditary cancer predisposition syndrome. A single pathogenic MSH2 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 MSH2 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.

No additional pathogenic variants were identified in the targeted genes by sequencing or by deletion/duplication analysis. 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 MSH2 c.2113delG; p.Val705TrpfsTer5 variant has been described in the literature in at least multiple families affected with Lynch syndrome (Domingo, 2004; Jeon, 1996; Moslein, 1996; Nilbert, 2009) and was observed to segregate with disease in at least one family (Jeon, 1996). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant causes a frameshift by deleting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Considering available information, this variant is classified as pathogenic.

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

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RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At risk adult family members should be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Counseling for potential reproductive risk associated with CMMRD syndrome is recommended (NCCN Guidelines).

COMMENTS
Likely benign and benign variants are not reported.

REFERENCES
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (1.2021). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.

Domingo E, et al. BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet. 2004;41(9):664-8.

Jeon HM, et al. Mutation of the hMSH2 gene in two families with hereditary nonpolyposis colorectal cancer. Hum Mutat. 1996;7(4):327-33.

Moslein G, et al. Microsatellite instability and mutation analysis of hMSH2 and hMLH1 in patients with sporadic, familial and hereditary colorectal cancer. Hum Mol Genet. 1996;5(9):1245-52.

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.

Wimmer K, 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]

Test Information

i1: LS Interp

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.

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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 of exon 9 only; sequencing is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of MLH1, MSH2, and MSH6 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. Multiplex ligation-dependent probe amplification (MLPA) of the targeted genes, including the MHS2 10Mb inversion of exons 1-7. Analysis of the PMS2 gene was performed by bidirectional Sanger sequencing of coding regions and the respective exon-intron boundaries as well as MLPA.

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

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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.