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

Physician: Doctor, Example

Patient: Patient, Example

DOB	7/30/2000
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

APC- and MUTYH-Associated Polyposis Panel, Sequencing and Deletion/Duplication

ARUP test code 3004407

APCMYH Specimen	Whole Blood

APCMYH Interp

Positive

RESULT
One pathogenic variant was detected in the APC gene.

PATHOGENIC VARIANT
Gene: APC (NM_000038.6)
Nucleic Acid Change: c.3183_3187del; Heterozygous
Amino Acid Alteration: p.Gln1062Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.3183_3187del; p.Gln1062Ter, was detected in the APC gene by massively parallel sequencing. Pathogenic APC variants are inherited in an autosomal dominant manner and are associated with familial adenomatous polyposis (FAP; MIM: 175100), attenuated FAP, or gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), which all predispose individuals to gastrointestinal polyposis and cancer. 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.

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

Evidence for variant classification:
The APC c.3183_3187del; p.Gln1062Ter variant (rs587779352) is reported in several individuals with familial adenomatous polyposis (Lee 2022, Miyoshi 1992, Papp 2016), and is reported in ClinVar (Variation ID: 88913). This variant is only found on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant causes a frameshift by deleting five nucleotides, so it 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.

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 APC variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS

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

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
Lee JK et al. Necessity of multiplex ligation probe amplification in genetic tests: Germline variant analysis of the APC gene in familial adenomatous polyposis patients. Cancer Genet. 2022 Apr;262-263:95-101. PMID: 35189564.

Miyoshi Y et al. Germ-line mutations of the APC gene in 53 familial adenomatous polyposis patients. Proc Natl Acad Sci U S A. 1992 May 15;89(10):4452-6. PMID: 1316610.

National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (2.2022): https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.

Papp J et al. Contribution of APC and MUTYH mutations to familial adenomatous polyposis susceptibility in Hungary. Fam Cancer. 2016 Jan;15(1):85-97. PMID: 26446593.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: APC- and MUTYH-Associated Polyposis Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: APC-associated polyposis conditions include: familial adenomatous polyposis (FAP), attenuated FAP (AFAP), and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). FAP: Development of hundreds to thousands of adenomatous colonic polyps beginning in early adolescence; lifetime risk for cancer in untreated individuals is 100 percent. AFAP: Fewer colonic adenomatous polyps (average of 30), which are more proximally located and cancer generally occurs at a later age. MUTYH-associated polyposis (MAP): Development of tens to hundreds of adenomatous colonic polyps with the mean age of presentation at around 50 years.

EPIDEMIOLOGY: The prevalence of FAP has been estimated to be between 1 in 6,850 to 1 in 31,250 live births. Approximately 0.5 percent of colorectal cancer (CRC) cases are caused by FAP. The prevalence of MAP is estimated to be between 1 in 20,000 to 1 in 60,000 individuals. MAP is estimated to account for 0.7 percent of all CRC.

CAUSE: A single pathogenic germline variant in the APC gene is causative for any one of the APC-associated polyposis conditions. Biallelic pathogenic germline variants in the MUTYH gene are causative for MAP.

INHERITANCE: FAP/APC-associated polyposis conditions: Autosomal dominant. MAP: Autosomal recessive.

PENETRANCE: 100 percent in untreated individuals with FAP. The penetrance of AFAP and MAP may be lower, and GAPPS is unknown.

CLINICAL SENSITIVITY: Approximately 93 percent for classic FAP and less than 30 percent for AFAP. Approximately 99 percent for MAP.

GENES TESTED: APC (NM_000038, NM_001127511 Exon 1b only), MUTYH (NM_001128425)

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 confirm reported variants. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

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. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of familial adenomatous polyposis (FAP), other APC-associated polyposis conditions, or MUTYH-associated polyposis. A negative result does not exclude all genetic diagnoses. This test only detects variants within the coding regions and intron-exon boundaries of the APC and MUTYH 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. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. 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) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
APCMYH Specimen	23-091-109549	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
APCMYH Interp	23-091-109549	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