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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1959
Sex:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

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.3920_3924del; Heterozygous
Amino Acid Alteration: p.Ile1307ArgfsTer6
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.3920_3924del; p.Ile1307ArgfsTer6, 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; OMIM(R)), 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.3920_3924del; p.Ile1307ArgfsTer6 variant (rs1064794229, ClinVar Variation ID 419999) is reported in the literature in individuals with familial adenomatous polyposis (Kerr 2013, Nieminen 2020). In addition, alternative changes at the same amino acid location also leading to frameshift, and several other downstream loss-of-function APC variants are also reported in individuals with familial adenomatous polyposis (Friedl 2005, Kerr 2013, Nilbert 2009, Plawski 2004, Thirlwell 2010), colorectal cancer (Manirakiza 2008), or colorectal adenomas (De Benedetti 1994). 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 5 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
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, Endometrial, and Gastric (3.2024): https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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Nieminen TT et al. Thyroid Carcinomas That Occur in Familial Adenomatous Polyposis Patients Recurrently Harbor Somatic Variants in APC, BRAF, and KTM2D. Thyroid. 2020 Mar;30(3):380-388. PMID: 32024448.

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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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
APCMYH Specimen	25-022-402173	1/16/2025 9:18:00 AM	1/22/2025 8:03:23 PM	1/30/2025 12:26:00 PM
APCMYH Interp	25-022-402173	1/16/2025 9:18:00 AM	1/22/2025 8:03:23 PM	1/30/2025 12:25:00 PM

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