Familial Adenomatous Polyposis Panel: (APC) Sequencing and Deletion/Duplication, (MUTYH) 2 Mutations
ARUP test code 2004915

FAP Panel Specimen: Whole Blood

FAP Panel Interp

<table>
<thead>
<tr>
<th>Positive*</th>
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<tbody>
<tr>
<td>TEST PERFORMED - 2004915</td>
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<tr>
<td>TEST DESCRIPTION - Familial Adenomatous Polyposis Panel: (APC) Sequencing and Deletion/Duplication, (MUTYH) 2 Mutations</td>
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<tr>
<td>INDICATION FOR TEST - Confirm Diagnosis</td>
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<tr>
<td>RESULT</td>
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<tr>
<td>One pathogenic variant was detected in the APC gene.</td>
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<td>DNA VARIANT</td>
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<tr>
<td>Classification: Pathogenic</td>
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<td>Gene: APC</td>
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<tr>
<td>Nucleic Acid Change: c.5826_5829delCAGA; Heterozygous</td>
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<tr>
<td>Amino Acid Alteration: p.Asp1942fs</td>
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|INTERPRETATION|
|One copy of a pathogenic variant, c.5826_5829delCAGA; p.Asp1942fs, was detected in the APC gene by sequencing. Pathogenic APC variants are causative for a spectrum of polyposis conditions that include familial adenomatous polyposis (FAP), attenuated-FAP and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). In addition to a predisposition to colorectal cancer, individuals harboring a pathogenic APC variant are also at risk for extracolonic cancers. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals; however, not all cancer risks associated with the APC gene are well defined (NCCN version 2.2019). Other genetic/environmental factors may also influence an individual’s risk of developing cancer. This individual’s offspring have a 50 percent risk of inheriting the pathogenic variant.|

No pathogenic variants were detected by deletion/duplication analysis of the APC gene. Targeted sequencing for two common pathogenic MUTYH (formerly MYH) gene variants, Y179C (also known as Y165C) and G396D (also known as G382D), was negative.

Evidence for variant classification: The APC c.5826_5829delCAGA; p.Asp1942fs variant (rs864622228), also known as 5824delGACA and 5844_5847del4, is reported in the literature in multiple individuals and several large families affected with familial adenomatous polyposis (Bisgaard 2004, Lamllum 2000, Scott 1996, Vieira 2015). This variant is reported in ClinVar (Variation ID: 219743), and is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is

H=High, L=Low, *=Abnormal, C=Critical
not a common polymorphism. This variant results in a premature termination codon in the last exon of the APC gene. While this may not lead to nonsense-mediated decay, it is expected to create a truncated protein missing the last 902 amino acids. Based on available information, this variant is considered pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered targeted testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequences: GenBank # NM_001127511.2 (APC exon 1B); NM_001127510.2 (APC); NM_001128425.1 (MUTYH)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
Bisgaard ML et al. Mutation analysis of the adenomatous polyposis coli (APC) gene in Danish patients with familial adenomatous polyposis (FAP). Hum Mutat. 2004 May;23(5):522.

This result has been reviewed and approved by Steven Steinberg, Ph.D.
Background Information for Familial Adenomatous Polyposis Panel: (APC) Sequencing and Deletion/Duplication, (MUTYH) 2 Mutations:

CHARACTERISTICS OF APC-ASSOCIATED POLYPOSI S:
Familial Adenomatous Polyposis (FAP): Development of hundreds to thousands of adenomatous colonic polyps beginning in early adolescence; lifetime risk for cancer is 100 percent. Additional findings may include dental anomalies, polyps of the gastric fundus and duodenum, and congenital hypertrophy of the retinal pigment epithelium (CHRPE).
Attenuated FAP: Fewer colonic adenomatous polyps (average of 30), which are more proximally located and cancer generally occurs at a later age; lifetime risk for cancer is 70 percent.
Gardner syndrome: Multiple colonic adenomatous polyps along with osteomas, desmoid tumors, and soft tissue tumors.
INCIDENCE: Less than 1 percent of colorectal cancer cases.
INHERITANCE: Autosomal dominant.
CAUSES: Pathogenic APC gene mutations.
CLINICAL SENSITIVITY: Approximately 95 percent for classic FAP and less than 30 percent for attenuated FAP.
METHODOLOGY: Bidirectional sequencing of the APC coding region and intron-exon boundaries. Multiplex ligation-dependent probe amplification (MLPA) to detect large APC coding region deletions or duplications.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. APC regulatory region and deep intronic mutations will not be detected. Deletion/duplication breakpoints will not be determined. This assay is not designed to detect somatic variants associated with malignancy. Interpretation of this test result may be impacted if the patient has had an allogenic stem cell transplantation.

CHARACTERISTICS OF MUTYH-ASSOCIATED POLYPOSI S (MAP):
Development of colonic polyps (10-100) with the age of diagnosis occurring in the third decade or older.
INCIDENCE: Less than 1 percent of colorectal cancer cases.
INHERITANCE: Autosomal recessive.
CAUSES: Pathogenic biallelic MUTYH gene mutations.
CLINICAL SENSITIVITY: 85 percent of MUTYH mutations in Caucasians.
METHODOLOGY: Targeted testing for the MUTYH mutations c.494A>G (Y165C) and c.1145G>A (G382D) by PCR and bidirectional sequencing.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Mutations in the MUTYH gene, other than Y165C and G382D, are not evaluated.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

H=High, L=Low, *=Abnormal, C=Critical
## VERIFIED/REPORTED DATES

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