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

Familial adenomatous polyposis (FAP) is an APC-associated polyposis condition caused by pathogenic variants in the APC gene resulting in the development of hundreds to thousands of adenomatous colonic polyps beginning in early adolescence. The lifetime risk for colorectal cancer (CRC) in individuals with FAP is 100%. Additional symptoms may include dental anomalies, polyps of the gastric fundus and duodenum, and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Pathogenic APC variants may also cause other related polyposis conditions, including attenuated FAP (AFAP) or gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).

MUTYH-associated polyposis (MAP), caused by biallelic pathogenic variants in the MUTYH gene, can result in the development of colon polyps that are less numerous (typically 10-100s) and is often diagnosed later in life. Genetic testing may be used to assess individuals at risk for FAP, other APC-associated polyposis conditions, or MAP due to a suggestive personal or family history.

Disease Overview

Associated Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Polyp and Cancer Characteristics</th>
<th>Age of Onset</th>
<th>Other Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>Hundreds to thousands of adenomatous colonic polyps may develop</td>
<td>Symptom onset at 7-36 years (generally early adolescence)</td>
<td>Dental anomalies</td>
</tr>
<tr>
<td></td>
<td>Polyps may develop in gastric fundus and duodenum</td>
<td>Mean age of CRC diagnosis is 39 years in untreated individuals</td>
<td>CHRPE</td>
</tr>
<tr>
<td></td>
<td>Without preventive colectomy, all individuals will develop CRC</td>
<td></td>
<td>Osteomas, soft tissue tumors, desmoid tumors</td>
</tr>
<tr>
<td>AFAP</td>
<td>Fewer colonic polyps than FAP (10-100s, with an average of 30)</td>
<td>Cancer occurs later than in FAP</td>
<td>Extracolonic manifestations are variable</td>
</tr>
<tr>
<td></td>
<td>More proximally located polyps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAPPS (associated with pathogenic variants in promoter 1B of the APC gene)</td>
<td>Gastric fundic gland polyposis and increased risk for gastric cancer</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Limited colonic involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (biallelic pathogenic MUTYH variants)</td>
<td>10 to a few hundred colonic adenomatous polyps</td>
<td>Third decade or later</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Source: Jaspers, 2017; Nielsen, 2021

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

APC- and MUTYH-Associated Polyposis Panel, Sequencing and Deletion/Duplication 3004407

Method: Massively Parallel Sequencing

- Preferred diagnostic or predictive test for APC-associated polyposis conditions (FAP, AFAP, GAPPS, and MAP).
- Testing minors for adult-onset conditions is not recommended; testing will not be performed in minors without prior approval. For additional information, please contact an ARUP genetic counselor at 800-242-2787 ext. 2141.
- If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.
Genetics

Genes

*APC* (NM_000038, NM_001127511 Exon 1b only) and *MUTYH* (NM_001128425)

For more information, see the [Genes Tested](#) table

Penetrance

Classic FAP: 100% incidence of CRC in untreated individuals\(^1\)

MAP:

- 43-63% incidence of CRC by age 60\(^2\)
- 80-90% lifetime risk of CRC\(^2\)

Etiology

FAP is estimated to account for 0.5% of CRC cases.\(^1\)

MAP is estimated to account for 0.7% of all CRC cases.\(^2\)

Prevalence

FAP: Approximately 1 in 6,850 to 1 in 31,250 individuals have FAP.\(^1\)

MAP: Approximately 1 in 20,000 to 1 in 60,000 individuals have MAP; approximately 1% of White individuals are predicted to carry a single pathogenic *MUTYH* variant.\(^2\)

Inheritance

*APC* is autosomal dominant.\(^1\)

*MUTYH* is autosomal recessive.\(^2\)

De Novo Variants

*APC*: 20-25% of individuals with FAP have a de novo pathogenic variant.\(^3\)

- 20% of individuals with apparent de novo variants in *APC* have somatic mosaicism.\(^1\)

Test Description

See the [Genes Tested](#) table for genes included in the panel.

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS, also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and, in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.
Clinical Sensitivity

Classic FAP: approximately 93%\(^4\)

- ≤90% of APC pathogenic variants detected by sequencing\(^1\)
- Approximately 8-12% of APC pathogenic variants detected by deletion/duplication testing\(^5,6\)

Attenuated FAP: <30%\(^7\)

GAPPS: unknown\(^1\)

MAP:

- Approximately 99% of pathogenic MUTYH variants detected by full gene sequencing\(^2\)
- <1% of pathogenic MUTYH variants detected by deletion/duplication analysis\(^2\)

Analytical Sensitivity

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate(^a) (%) and 95% Credibility Region (%)</th>
<th>Analytical Specificity (NPA) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Deletions 1-10 bp(^b)</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp(^b)</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level(^c) Deletions</td>
<td>97.8 (90.3-99.8) [2 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level(^c) Duplications</td>
<td>83.3 (56.4-96.4) [3 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

\(^a\)Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

\(^b\)Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

\(^c\)In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Testing Strategy

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy as sensitivity for mosaic variants is low with methodology used for germline assays
- Individuals with hematologic malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen.
  - Testing of cultured fibroblasts is required for accurate interpretation of test results.

Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Single pathogenic variant in APC gene</td>
<td>Predictive of FAP or other APC-associated polyposis condition</td>
</tr>
<tr>
<td></td>
<td>Two pathogenic variants in MUTYH gene on opposite chromosomes</td>
<td>Predictive of MAP</td>
</tr>
<tr>
<td></td>
<td>Single pathogenic MUTYH variant</td>
<td>Individual is a carrier of MAP and may be affected if another unidentified pathogenic MUTYH variant is present on the opposite chromosome</td>
</tr>
</tbody>
</table>
Possible increased risk for cancer has been associated with a single pathogenic MUTYH variant, but is not well defined

A negative result does not exclude a diagnosis of FAP or MAP.
Diagnostic errors can occur due to rare sequence variations.
Interpretation of this test result may be impacted if this patient has had an allogenic stem cell transplantation.
The following will not be evaluated:
- Variants outside the coding regions and intron-exon boundaries of targeted genes
- Regulatory region and deep intronic variants
- Breakpoints of large deletions/duplications
The following may not be detected:
- Deletions/duplications/insertions of any size by massively parallel sequencing
- Large duplications less than 3 exons in size
- Noncoding transcripts
- Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
- Low-level somatic variants

Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM Number</th>
<th>Disorder/Associated Cancer(s)/Tumor(s)</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>611731</td>
<td>FAP, AFAP, GAPPS</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colorectal adenomas and cancer, duodenal adenomas and cancer, fundic gland polyps, osteomas, thyroid, pancreas, and others</td>
<td></td>
</tr>
<tr>
<td>MUTYH</td>
<td>604933</td>
<td>Associated cancer(s)/tumor(s): breast,a colorectala</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated cancer(s)/tumor(s): colorectal adenomas and cancer, duodenal adenomas and cancer</td>
<td></td>
</tr>
</tbody>
</table>

aAssociation is suggested but not well-established at this time.
AD, autosomal dominant; AR, autosomal recessive

References


## Additional Resources


## Related Information

Colorectal (Colon) Cancer
Hereditary Gastrointestinal Cancer Panels

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84105
(801) 583-2787 | (800) 583-2787 | aruplab.com | arupconsult.com
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