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

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

Source: Jasperson, 2017[1]; Nielsen, 2021[2]

Tests to Consider

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).

Related Tests

Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication 2013449

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray/Sequencing/Multiplex Ligation-dependent Probe Amplification

Recommended test to confirm a diagnosis of hereditary gastrointestinal (GI) cancer in individuals with a personal or family history of GI cancer and/or polyposis

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- Useful when a pathogenic familial variant identifiable by sequencing is known
- A copy of a relative's lab report is REQUIRED.

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

- Use to asses for large deletion/duplication previously identified in a family member
- A copy of a relative's lab report is REQUIRED.

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[2]; 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

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytical Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] Deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] Duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[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.
- When a relative has a previously identified pathogenic variant, see Familial Mutation, Targeted Sequencing (2001961).

Results

Result	Variant(s) Detected	Clinical Significance
Positive	Single pathogenic variant in *APC* gene	Predictive of FAP or other *APC*-associated polyposis condition
	Two pathogenic variants in *MUTYH* gene on opposite chromosomes	Predictive of MAP

Result	Variant(s) Detected	Clinical Significance
	Single pathogenic *MUTYH* variant	Individual is a carrier of MAP and may be affected if another unidentified pathogenic *MUTYH* variant is present on the opposite chromosome Possible increased risk for cancer has been associated with a single pathogenic *MUTYH* variant, but is not well defined
Negative	No pathogenic variants in either *APC* or *MUTYH* gene	Does not rule out FAP, other *APC*-associated polyposis conditions, or MAP
Inconclusive	Variant of uncertain clinical significance detected	Uncertain

Limitations

- 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

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
APC	611731	FAP AFAP GAPPS Associated cancer(s)/tumor(s): colorectal adenomas and cancer, duodenal adenomas and cancer, fundic gland polyps, osteomas, thyroid, pancreas, and others	AD
MUTYH	604933	Associated cancer(s)/tumor(s): breast,[a] colorectal[a]	AD
		MAP Associated cancer(s)/tumor(s): colorectal adenomas and cancer, duodenal adenomas and cancer	AR

[a]Association is suggested but not well-established at this time.

AD, autosomal dominant; AR, autosomal recessive

References

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5. Aretz S, Stienen D, Uhlhaas S, et al. Large submicroscopic genomic APC deletions are a common cause of typical familial adenomatous polyposis. *J Med Genet*. 2005;42(2):185-192.

6. Bunyan DJ, Eccles DM, Sillibourne J, et al. Dosage analysis of cancer predisposition genes by multiplex ligation-dependent probe amplification. *Br J Cancer*. 2004;91(6):1155-1159.

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Additional Resources

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Lubbe SJ, Di Bernardo MChiara, Chandler IP, et al. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. *J Clin Oncol*. 2009;27(24):3975-3980.

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Related Information

Colorectal Cancer

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Content Review November 2021 | Last Update February 2022