Familial Adenomatous Polyposis (*APC)* Sequencing and Deletion/Duplication and (*MUTYH)* 2 Mutations

Indications for Ordering

- Confirm clinical diagnosis of
  - Familial adenomatous polyposis (FAP)
  - Attenuated FAP
  - Turcot syndrome
  - Gardner syndrome
  - Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)
  - *MUTYH*-associated polyposis (MAP)
- Assess individuals at risk for *APC*-associated polyposis or MAP due to family history in the absence of a known pathogenic familial variant

Test Description

- *APC* gene
  - Bidirectional sequencing of entire coding region and intron/exon borders
  - Multiplex ligation-dependent probe amplification to detect large deletions/duplications
- *MUTYH* gene
  - Bidirectional targeted sequencing for two common pathogenic variants
    - c.494A>G (p.Y165C)
    - c.1145G>A (p.G382D)

Tests to Consider

Primary test

Familial Adenomatous Polyposis Panel: (*APC*) Sequencing and Deletion/Duplication, (*MUTYH*) 2 Mutations 2004915
- Preferred diagnostic or predictive test for FAP and MAP

Familial Adenomatous Polyposis (*APC*) Sequencing 2004863
- Acceptable diagnostic or predictive test for FAP
- For classic FAP, consider *APC* sequencing and deletion/duplication testing

Related tests

MUTYH-Associated Polyposis (*MUTYH*) 2 Mutations 2004911
- Acceptable diagnostic or predictive test for MAP in Northern European Caucasians
  - For non-Caucasians, order *MUTYH* sequencing
- Only two targeted pathogenic *MUTYH* variants are tested
  - Y165C
  - G382D

MUTYH-Associated Polyposis (*MUTYH*) Sequencing 2006191
- Diagnostic or predictive test for MAP
- Use if one or no pathogenic variant is found with *MUTYH*-associated polyposis 2 mutations test

MUTYH-Associated Polyposis (*MUTYH*) 2 Mutations with Reflex to Sequencing 2006307
- Preferred diagnostic or predictive test for MAP in Northern European Caucasians
  - For non-Caucasians, order *MUTYH* gene sequencing
- *MUTYH* sequencing will be performed if two pathogenic variants are not detected by targeted testing for Y165C and G382D

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence/prevalence

- Colorectal cancer (CRC) – ~140,000/year in U.S.
  - Lifetime risk of developing CRC – 6%
  - FAP accounts for ~0.5% of CRC cases
- Most CRC caused by pathogenic somatic variants
  - Not hereditary
- ~1% of Caucasians are predicted to carry a pathogenic *MUTYH* variant

Symptoms

FAP
- Development of hundreds to thousands of adenomatous colonic polyps
- Dental anomalies
- Polyps of gastric fundus and duodenum
- Congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Begins generally during early adolescence
- Overall age range of 7-36 years
- Without a preventive colectomy, all individuals with FAP will develop colon cancer during their lifetime
- Mean age at time of diagnosis is 39 years

Attenuated FAP differs from FAP
- Typically fewer polyps
  - 10-100, with an average of 30
- More proximally located polyps
- Cancer generally occurs at a later age

Gardner syndrome
- Occurs in 20% of families with classic FAP
- Associated with
  - Benign osteomas
  - Desmoid tumors
  - Soft-tissue tumors

Turcot syndrome
- Colon polyps
- Central nervous system tumors
- Associated with medulloblastoma
- Often caused by pathogenic variants in *APC* gene
- Turcot with glioblastoma multiforme is usually caused by pathogenic variants in a mismatch repair gen

GAPPS
- Associated with pathogenic variants in promoter 1B of the *APC* gene
- Fundic gland polyposis
- Increased risk for gastric cancer

MAP
- 10-100 polyps
- ~20-30% of patients with 10-100 polyps have biallelic pathogenic *MUTYH* variants
- Age of onset is third decade or later

Genetics

Genes – *APC, MUTYH*

Inheritance
- *APC* – autosomal dominant
- *MUTYH* – autosomal recessive

Penetrance

Classic FAP – 100% in untreated individuals

Function
- *APC* pathogenic variants cause
  - FAP
  - Attenuated FAP
  - Gardner syndrome
  - Turcot syndrome
- All diseases predispose individuals to CRC
- *MUTYH* gene
  - Pathogenic variants may cause MAP

De novo variants

APC – 25% of cases

Pathogenic variants

Pathogenic variants in *APC* gene may correlate with disease severity

Test Interpretation

Sensitivity/specificity
- Analytical sensitivity/specificity – 99% for *APC* and *MUTYH*
- Clinical sensitivity
  - Classic FAP – ~95%
    - ~90% of pathogenic variants detected by sequencing (Jasperson, 2014; Lagarde, 2010)
    - ~8-12% of pathogenic variants detected by deletion/duplication testing (Aretz, 2005; Bunyan, 2004)
  - Attenuated FAP – <30% (Lefevre, 2006)
  - GAPPS – unknown
  - MAP
    - 85% of pathogenic *MUTYH* variants in Northern European Caucasians detected by the 2 pathogenic variants test (Y165C and G382D) (Aretz, 2013; Inra, 2015)
    - 98% of pathogenic *MUTYH* variants detected by full gene sequencing (Out, 2010; Nielsen, 2015)

Results
- Positive
  - Identification of a single pathogenic variant in *APC* gene
    - Predictive of FAP or *APC*-associated polyposis
  - Detection of two pathogenic *MUTYH* variants on opposite chromosomes
    - Predictive of MAP
  - Identification of a single pathogenic *MUTYH* variant
    - Individual is a carrier of MAP
    - Individual could be affected if another unidentified pathogenic *MUTYH* variant is present on the opposite chromosome
- Negative
  - No pathogenic variants were detected in *APC* or *MUTYH* gene
  - Does not rule out FAP, *APC*-associated polyposis, or MAP
- Inconclusive – variant(s) of unknown clinical significance may be detected

Limitations
- *APC* gene
  - Deep intronic or regulatory region variants will not be identified
  - Breakpoints of large deletions/duplications will not be determined
- Only two pathogenic *MUTYH* variants will be tested
  - Y165C
  - G382D
- Diagnostic errors can occur due to rare sequence variations

References

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