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 200463
  - Acceptable diagnostic or predictive test for FAP
  - For classic FAP, consider APC sequencing and deletion/duplication testing

- 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**

- Use 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 gene

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