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
  - 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 gene

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)
  - MAP
    - 85% of pathogenic MUTYH variants in Northern European Caucasians detected by the 2 mutations 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 intrinsic 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