MUTYH-Associated Polyposis

Indications for Ordering

- Confirm clinical diagnosis of *MUTYH*-associated polyposis (MAP)
- Test individuals at risk for MAP due to family history in the absence of a known familial variant

Test Description

Bidirectional sequencing of entire coding region and intron/exon borders of *MUTYH* gene

Tests to Consider

Primary test

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

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 pathogenic *MUTYH* variants are tested
  - c.494A>G (p.Y165C)
  - c.1145G>A (p.G382D)

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

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%
  - MAP accounts for <1% of CRC cases
- Most CRC caused by pathogenic somatic variants
  - Not hereditary
- ~1% of Caucasians are predicted to carry a pathogenic *MUTYH* variant

Age of onset – third decade or later; mean is 48 years

Symptoms
- MAP is characterized by multiple colorectal adenomas and an increased risk for colorectal cancer
- ~20-30% of patients with 10-100 polyps have biallelic pathogenic *MUTYH* variants

Diagnostic issues
- FAP
  - Caused by pathogenic variants in *APC* gene
- MAP
  - Caused by pathogenic variants in *MUTYH* gene

Recommended follow-up testing
- Colorectal surveillance is recommended, beginning at 18 years, for individuals with biallelic pathogenic variants
- *MUTYH* sequencing is recommended for symptomatic individuals with only one identifiable pathogenic *MUTYH* variant

Genetics

Gene – *MUTYH*

Inheritance – autosomal recessive

Penetrance
Proportion of individuals with biallelic pathogenic variants who develop colorectal cancer
- 20% by age 50
- 43% by age 60 (Lubbe, 2009)

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - 85% of pathogenic *MUTYH* variants in Northern European Caucasians are detected by the 2 mutation test (Y165C and G382D) (Aretz, 2013; Inra, 2015)
  - 98% of pathogenic *MUTYH* variants are detected by full gene sequencing (Astrid, 2010; Nielsen, 2015)
- Analytical sensitivity/specificity – 99%

Results

- Positive
  - Two pathogenic *MUTYH* variants detected on opposite chromosomes
    - Predictive for MAP
  - One pathogenic *MUTYH* variant detected
    - Individual is a carrier of MAP
    - Individual could be affected if another undetected pathogenic *MUTYH* variant is present on the opposite chromosome
- Negative
  - No pathogenic *MUTYH* variants detected
    - MAP is unlikely, but not excluded
- Inconclusive
  - Variant(s) of uncertain significance may be detected

Limitations

- Not detected
  - Large deletions or duplications
  - Deep intronic, regulatory region, or promoter pathogenic variants
- Diagnostic errors can occur due to rare sequence variations

References

- Aretz S, Genuardi M, et al. Clinical utility gene card for: MUTYH-associated polyposis (MAP), autosomal recessive colorectal adenomatous polyposis, multiple colorectal adenomas, multiple adenomatous polyps (MAP) - update 2012. Eur J Hum Genet. 2013;21(1)
- Inra JA, Steyerberg EW, et al. Racial variation in frequency and phenotypes of APC and MUTYH mutations in 6,169 individuals undergoing genetic testing. Genet Med. 2015;17:815-821
- Lubbe SJ, Di Bernardo MC, 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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