MUTYH Associated Polyposis Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is MUTYH-associated polyposis

Definition

MUTYH-associated polyposis (MAP) is an inherited colorectal cancer syndrome caused by mutations in the MUTYH gene (also called MYH). MAP is estimated to account for 0.7% of all colorectal cancer.¹

- MAP clinical findings overlap those of familial adenomatous polyposis (FAP) and attenuated FAP (AFAP). Affected patients most often have fewer than 100 adenomas, but cases of hundreds and occasionally over 1000 polyps have been reported.¹² Hyperplastic and sessile serrated, and traditional serrated adenomatous polyps have also been seen in individuals with MAP, although adenomas remain the most common polyp type in MAP.¹³ Duodenal adenomas occur in 17-25% of individuals with MAP and gastric polyps have been reported in about 11%.¹³,⁴ Additionally, approximately one third of individuals with MAP have been described with colorectal cancer and no polyps or only a few polyps.¹

- Up to 26% of people who meet clinical diagnostic criteria for classic or attenuated FAP, but have normal FAP genetic test results, will have a MAP mutation.¹

- Because MAP is not clinically distinguishable from FAP or AFAP, the identification of two MUTYH mutations is required to make a MAP diagnosis.¹⁵

- Adenomas and colorectal cancer tend to present later than FAP. The diagnosis of colorectal cancer is often 50 years (range of 45-59 years).¹² The lifetime risk for colorectal cancer in individuals with MAP is 43 to 100% in the absence of timely surveillance.¹ There is also an estimated 4-5% lifetime risk for duodenal cancer.¹³
• Unlike FAP, MAP is inherited in an autosomal recessive manner — both copies of the MUTYH gene must have a mutation to be affected. This means that siblings are the only relatives likely to be affected in the family history (i.e., you do not see inheritance from parent to child as with FAP).

Test information

• **MUTYH Targeted Mutation Analysis:** Two MUTYH mutations are particularly common (Y165C and G382D) and account for over 80% of MUTYH mutations in Caucasians of Northern European descent.\(^6\) It is estimated that 1%-2% of the general northern European population is a carrier for a MUTYH mutation.\(^1\) Some laboratories test for only these two mutations or offer reflex options that begin with these two mutations and proceed to full gene sequencing if two mutations are not found.

• **MUTYH Sequencing Analysis:** MUTYH full sequencing analysis analyzes the entire gene for mutations. It is typically done in reflex to negative results from targeted mutation analysis.

• **MUTYH Deletion/Duplication Analysis:** If sequencing does not find two mutations, large gene deletion/duplication analysis can be performed. It remains unknown what percentage of MAP is due to large deletions/duplications/rearrangements in the gene and thus are detectable only with this technology. However, large deletions have been reported.\(^1,7,8\)

• **MUTYH Known Familial Mutation Analysis:** Once the mutations that run in the family are known, other relatives can have testing for only those mutations. This is more accurate and cost-effective.

• **Multi-gene Panel Test:** A multi-gene panel that includes MUTYH and other polyposis genes may also be considered.\(^1\)

Guidelines and evidence

• Guidelines from the National Comprehensive Cancer Network (NCCN, 2018) on High-Risk Colorectal Assessment states the following:\(^2\)
  
  o MUTYH testing criteria:
    
    ▪ “Personal history of >10 adenomas”
    
    ▪ “Individual meeting criteria 1 or 3 (NCCN, 2017) for Serrated Polyposis Syndrome (SPS) [formerly known as hyperplastic polyposis] with at least some adenomas.” (see below)
    
    ▪ “Known deleterious MUTYH mutation(s) in the family”

  o SPS clinical diagnostic criteria:
i. “At least 5 serrated polyps (includes hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas) proximal to the sigmoid colon with 2 or more of these being >10mm."

ii. “Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis.”

iii. “At least 20 serrated polyps of any size, but distributed throughout the colon.”

Footnotes:

- “When colonic polyposis is present in a single person with a negative family history, consider testing for a de novo APC mutation; if negative, follow with testing of MUTYH (targeted testing for the two common northern European founder mutations c.536A>G and c.1187G>A may be considered first followed by full sequencing if biallelic mutations are not found). When colonic polyposis is present only in siblings, consider recessive inheritance and test for MUTYH first. Order of testing for APC and MUTYH is at the discretion of the clinician.”

- “MUTYH genetic testing is not indicated based on a personal history of desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral CHRPE.”

- “Siblings of a patient with MAP are recommended to have site-specific genetic testing for the familial biallelic mutations. Children of an affected parent with MAP are recommended to have site-specific genetic testing for the familial mutation/s. If positive for one MUTYH mutation, full sequencing of MUTYH is recommended. Full sequencing of MUTYH also may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not be heterozygous for a MUTYH mutation, genetic testing in children is not necessary. If he or she is found to have a MUTYH mutation, testing for the familial mutations in the children is recommended.”

- “It is important to note that de novo mutations can occur in APC or MUTYH. Thus, when colonic polyposis is present in an individual with a negative family history, consideration should be given to genetic testing of APC, followed by testing of MUTYH if no APC mutation is found.”

All recommendations are category 2A.

- Evidence-based guidelines from the American College of Gastroenterology (ACG, 2009) state:9 “Patients with classic FAP, in whom genetic testing is negative, should undergo genetic testing for bi-allelic MUTYH mutations. Patients with 10 - 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, MUTYH associated polyposis” [Grade 2C: Weak recommendation, low-quality or very low-quality evidence].
Criteria
MUTYH Known Familial Mutation Analysis

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Testing:
  o No previous genetic testing for known MUTYH family mutation(s), AND

• Diagnostic or Predisposition Testing:
  o Two known MUTYH mutations in a sibling, or
  o Both parents with one or two known MUTYH mutations, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

MUTYH Targeted Mutation Analysis for Y179C and G396D Mutations

• Genetic Counseling
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Testing:
  o No previous MUTYH testing, and
  o No mutation detected on APC gene testing, if performed, AND

• Individual is of Northern European descent, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Clinical findings:
    ▪ > 10 cumulative adenomas, or
    ▪ At least two adenomas, AND
      • At least 5 serrated polyps proximal to the sigmoid colon (2 or more of >10mm), or
      • > 20 serrated polyps of any size, but distributed throughout the colon, AND
    o Recessive pattern of inheritance (e.g. family history positive for only an affected sibling), OR

• Testing for Presymptomatic/Asymptomatic Individuals:
  1,2
- Reproductive partner of a person with MAP (to determine if children at risk), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**MUTYH Sequencing**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous MUTYH full sequencing, and
  - Two mutations NOT identified through MUTYH targeted mutation analysis (Y179C and G396D) if performed, and
  - No mutation detected on APC gene testing, if performed, AND
- Diagnostic Testing for Symptomatic Individuals: 2,10
  - Clinical findings:
    - > 10 cumulative adenomas, or
    - At least two adenomas, AND
      - At least 5 serrated polyps proximal to the sigmoid colon (2 or more of >10mm), or
      - > 20 serrated polyps of any size, but distributed throughout the colon, AND
  - Recessive pattern of inheritance (e.g. family history positive for only an affected sibling), OR
- Testing for Presymptomatic/Asymptomatic Individuals: 1,2
  - Reproductive partner of a person with MAP (to determine if children at risk), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**MUTYH Deletion/Duplication Analysis**

- Genetic Counseling
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
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MUTYH full sequencing performed, and
- No mutations or only one mutation detected in MUTYH through any previous testing (founder mutation panel or full gene sequencing), and
- No mutation detected on APC gene testing, if performed, AND

- Diagnostic Testing for Symptomatic Individuals:2,10
  - Clinical findings:
    - > 10 cumulative adenomas, or
    - At least two adenomas, AND
      - At least 5 serrated polyps proximal to the sigmoid colon (2 or more of >10mm), or
      - > 20 serrated polyps of any size, but distributed throughout the colon, AND
  - Recessive pattern of inheritance (e.g. family history positive for only an affected sibling), OR
- Testing for Presymptomatic/Asymptomatic Individuals:1,2
  - Reproductive partner of a person with MAP (to determine if children at risk), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

References


