MUTYH-Associated Polyposis Genetic Testing

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Introduction

MUTYH-associated polyposis (MAP) genetic testing is addressed by this guideline.

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.

Procedures addressed by this guideline	Procedure codes
MUTYH deletion/duplication analysis	81479
MUTYH known familial mutation analysis	81403
MUTYH sequencing	81406
MUTYH targeted mutation analysis	81401

Criteria

Introduction

Requests for MUTYH-associated polyposis (MAP) testing are reviewed using the following criteria.

MUTYH Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation(s), AND
- Diagnostic or Predisposition Testing:

MUTYH

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  - Two known MUTYH mutations in a sibling, or
  - 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 p.Y179C and p.G396D Mutations

- 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 testing, and
  - No mutation detected on APC gene testing, if performed, AND
- Individual is of possible Northern European descent, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical findings:
    - At least 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:
  - Reproductive partner of a person with MAP-associated mutation(s) (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 (p.Y179C and p.G396D) if performed, and
  - No mutation detected on APC gene testing, if performed, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical findings:
    - At least 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:
    - Reproductive partner of a person with MAP-associated mutation(s) (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:
    - 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
    - Meets criteria for MUTYH full sequencing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

MUTYH testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is MUTYH-associated polyposis?

MUTYH-associated polyposis (MAP) is an inherited colorectal cancer syndrome characterized by the development of multiple colon polyps.[1] Individuals also have an increased chance to develop duodenal adenomas which may cause duodenal cancer.[1-3] Some studies have documented an increased risk for ovarian cancer and bladder cancer.[1] Additionally, there is "some evidence of an increased risk for breast and endometrial cancer. Additional reported features include thyroid nodules, benign adrenal lesions, jawbone cysts, and congenital hypertrophy of the retinal pigment epithelium."[1] At this time, management guidelines are available for colonic and duodenal manifestations.

Prevalence

MAP is estimated to account for 0.7% of all colorectal cancer, and the prevalence of MAP is estimated to be 1/20,000 to 1/60,000.[1] It is estimated that 1-2% of individuals in Northern Europe, Australia, and the United States have a single MUTYH mutation.[1]

MUTYH mutations "account for 10%-20% of classical FAP [Familial Adenomatous Polyposis] cases without an APC mutation and for 30% of AFAP [Attenuated Familial Adenomatous Polyposis] cases."[4]

Symptoms

MAP clinical findings overlap those of FAP and AFAP. Affected individuals most often have fewer than 100 adenomas, but cases of hundreds and occasionally over 1000 polyps have been reported.[1,2] Hyperplastic and sessile serrated, and traditional serrated adenomatous polyps have also been seen individuals with MAP, although adenomas remain the most common polyp type in MAP.[1,3] Duodenal adenomas occur in 17-34% of individuals with MAP and gastric polyps have been reported in about 11%.[1,3,4] Additionally, approximately one third of individuals with MAP have been described with colorectal cancer and no polyposis.[1]

Adenomas and colorectal cancer tend to present later than FAP. MAP is "characterized by a greatly increased lifetime risk of colorectal cancer (CRC) (43%-63% at age 60 years and a lifetime risk of 80%-90% in the absence of timely surveillance)."[1] There is also an estimated 4-5% lifetime risk for duodenal cancer.[1-3]

Cause

MAP is caused by mutations in the MUTYH gene (also called MYH).[1]

Inheritance

MAP is an autosomal recessive disorder.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

As MAP is not clinically distinguishable from FAP or AFAP, the identification of two MUTYH mutations is required to make a diagnosis of MAP.[1,5]

Two MUTYH mutations (p.Y165C and p.G382D) are particularly common and account for over 80% of MUTYH mutations in Caucasians of Northern European descent.[6] 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.

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]

Surveillance

For individuals with MAP, colonoscopy screening should begin at 25-30 years (earlier colonoscopy may be indicated based on family history). If the colonoscopy is negative, repeat colonoscopy should occur every 1-2 years.[2] For positive colonoscopy findings, the treatment and surveillance is dependent on polyp burden.[2] Additional recommended screening includes upper endoscopy with complete visualization of the ampulla of Vater beginning at 30-35 years.[2] If no duodenal polyps are detected, then repeat endoscopy occurs every 3 to 5 years. If duodenal polyps are detected, repeat endoscopy is dependent on the quantity and size of the polyps.[2]

"Chemoprevention may be considered in select patients, but options have not been studied specifically in MAP. Consider referral to a center with expertise for discussion of chemoprevention and surgical options, particularly for patients with a high polyp burden in the remaining rectum after colectomy."[2]

For individuals with a single MUTYH mutation, the recommended surveillance is dependent on the family history of colon cancer.[2]

- Individuals without a history of colorectal cancer and with a first-degree relative with colorectal cancer: colonoscopy screening every 5 years beginning at 40 years or 10 years prior to the age of the first-degree relative's diagnosis, whichever comes first. Colonoscopy may be repeated at more frequent intervals if indicated based on colonoscopy findings.
- Individuals without a history of colorectal cancer and with a second-degree relative with colorectal cancer or if there is no family history of colorectal cancer: there are no specific screening recommendations.

Test information

Introduction

Testing for MAP may include known familial mutation analysis, targeted mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutation analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the known mutation(s). However, if available, a targeted mutation panel that includes the familial mutation(s) may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American College of Gastroenterology

Evidence-based guidelines from the American College of Gastroenterology (ACG, 2015) stated:[9]

- "Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors (abdominal>peripheral), papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes. ... Genetic testing of patients with suspected adenomatous polyposis syndromes should include APC and MUTYH gene mutation analysis."

American Society of Clinical Oncology and European Society for Medical Oncology

The American Society of Clinical Oncology (ASCO, 2015) endorsed the European Society for Medical Oncology (ESMO, 2013) clinical practice guideline on hereditary colorectal cancer syndromes. This guideline stated:[10]

- "Patients with multiple colorectal adenomas (>10), should be considered for germline testing of APC and/or MUTYH."
- "Germline testing of MUTYH can be initiated by screening for the most common mutations ([p.]G396D, [p.]Y179C) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered."

American Society of Gastrointestinal Endoscopy

Consensus guidelines from the American Society of Gastrointestinal Endoscopy (ASGE, 2020) recommended:[11]

- "...genetic counseling and testing in patients with clinical polyposis defined as 10 or more adenomas found on single endoscopy and 20 or more adenomas during their lifetime." [low quality]
- "...genetic counseling and testing in all first-degree relatives of confirmed polyposis syndrome patients. ... suspected AFAP and MAP should be tested at age 18-20 years." [low quality]

National Comprehensive Cancer Network

Guidelines from the National Comprehensive Cancer Network (NCCN, 2025) stated:[2]

- MUTYH testing criteria:
  - At least 10 adenomas
  - Meets criteria for SPS [Serrated Polyposis Syndrome] and some adenomas. (see below)
  - Known deleterious MUTYH mutation(s) in the family
- SPS clinical diagnostic criteria:
  - "≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size."
  - ">20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum."
  - Note: "any histological subtype of serrated lesion/polyp (hyperplastic polyp, sessile serrated lesion without or with dysplasia, traditional serrated adenoma, and unclassified serrated adenoma) is included in the final polyp count. The polyp count is cumulative over multiple colonoscopies."
- "Siblings of a patient with MAP are recommended to have site-specific testing for the familial PVs [pathogenic variants]. Full sequencing of MUTYH may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a MUTYH PV [pathogenic variant], genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, comprehensive testing of MUTYH should be considered in the adult children. If the unaffected parent is found to have one MUTYH PV, testing the adult children for the familial MUTYH PVs is indicated."
- "When colonic polyposis is present only in the proband and/or in siblings, consider recessive inheritance or de novo APC gene mutations … Overall, the decision to order APC, MUTYH, or germline multi-gene testing including these genes should be at the discretion of the clinician."
- All recommendations are category 2A.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for MUTYH testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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