Familial Adenomatous Polyposis Genetic Testing

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Introduction

Genetic testing for familial adenomatous polyposis (FAP) 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
APC deletion/duplication analysis	81203
APC known familial mutation analysis	81202
APC sequencing	81201

Criteria

Introduction

Requests for genetic testing for familial adenomatous polyposis (FAP) are reviewed using the following criteria.

APC 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 Genetic Testing:
  - No previous genetic APC mutation testing that would detect the familial mutation, AND
- Diagnostic or Predisposition Testing:
  - Family History:

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    - Known family mutation in APC identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

APC Sequencing

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
    - No previous APC mutation testing, and
    - No known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
    - Personal history:
        - At least 10 cumulative adenomas (known or suspected diagnosis of FAP – 100 or more adenomas or attenuated FAP [AFAP] – 10 to 100 adenomas), or
        - A desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral congenital hypertrophy of retinal epithelium (CHRPE), 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, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
    - Family history:
        - First-degree relative of an individual in whom FAP has been clinically diagnosed or AFAP is considered (at least 10 but less than 100 polyps). (Note: Whenever possible, an affected family member should be tested first), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

APC Duplication/Deletion Analysis

- Genetic Counseling:

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

- Previous Genetic Testing:
  - No previous large rearrangement testing, and
  - Previous APC sequencing performed and no mutations found, and
  - No known familial mutation, and
  - Meets criteria for APC full sequencing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Other Considerations

Due to the risk of mosaicism, requests for testing capable of detecting low-level mosaicism (<10% VAF) after negative APC testing may be considered on a case-by-case basis when there is a high clinical suspicion for FAP/AFAP.

APC 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 Familial Adenomatous Polyposis?

Definition

Familial adenomatous polyposis (FAP) is an inherited colorectal cancer syndrome characterized by the development of numerous colorectal adenomatous polyps and an increased risk for colon cancer if left untreated. Affected individuals also have an increased risk for gastrointestinal polyps outside the colon, extracolonic malignancies, and non-malignant extracolonic manifestations.[1]

Prevalence

The prevalence of FAP varies and has been reported as 1/6,850 to 1/31,250.[1] Males and females are equally affected.

Symptoms

FAP is considered in an individual with 100 or more colorectal adenomatous polyps or in an individual with fewer than 100 polyps and a family member with FAP. Polyposis typically begins before age 35. Virtually all people with classic FAP will develop colorectal cancer without intervention.[1] Other clinical manifestations include:[1]

- Modestly increased risk for other malignancies including cancers of the thyroid, small bowel, stomach, liver (hepatoblastoma, typically seen in children under 5), pancreas, brain (medulloblastoma), and bile duct.
- Additional gastrointestinal manifestations including adenomatous polyps of the duodenum and stomach and gastric fundic gland polyps.
- Non-gastrointestinal manifestations including osteomas (often of the mandible or skull), dental abnormalities (supernumerary teeth, odontomas), desmoid tumors, soft tissue tumors (epidermoid cysts, fibromas), adrenal masses (adenomas), and congenital hypertrophy of retinal epithelium (CHRPE).[1] Isolated CHRPE may be found in the general population, but multiple or bilateral CHRPE in an at-risk family member may be suspicious for FAP.
- Attenuated FAP (AFAP) is a milder form of FAP characterized by a later onset of disease and fewer cumulative lifetime adenomas (ranging from 10 to <100).[2] Phenotypic expression of classic versus attenuated FAP is often variable within families. Colorectal cancer (CRC) onset is typically delayed by 10 to 20 years compared with individuals with FAP. Currently, there is no consensus regarding precise clinical diagnostic criteria for AFAP.[1,3,4]

Cause

Almost all cases of FAP are due to mutations in the adenomatous polyposis coli (APC) gene, a tumor suppressor gene.

- Most people inherit an APC mutation from an affected parent.
- Up to 1 in 4 people with FAP have a de novo mutation with no known affected family members.
- About 20% of simplex cases of FAP are caused by somatic mosaicism for APC mutations.[1]
- The parents of someone with FAP may also be unaffected or mildly affected due to germline and/or somatic mosaicism.[1]

Some genotype-phenotype correlations have been established. Surveillance and management should be focused on an "affected individual's phenotype and not based solely on genotype."[1]

Inheritance

FAP is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The diagnosis is established when a mutation is identified in the adenomatous polyposis coli (APC) gene in an individual with characteristic clinical findings.

- APC sequence analysis is used to identify disease-causing mutations in those clinically diagnosed with FAP/AFAP.[4-7] This testing will detect a mutation in up to 90% of individuals with clinically diagnosed FAP.[1] The mutation rate is lower for those with AFAP.[6] Testing may be considered for close relatives of someone with FAP when an affected relative is unavailable for testing. [6]
- APC deletion/duplication testing is typically performed in reflex to negative sequence analysis. Deletion/duplication testing detects an additional 8-12% of mutations in those with clinical suspicion of FAP.[1]

Surveillance

Management and prevention strategies for those affected with or at-risk for FAP/AFAP include annual colon screening (colonoscopy is preferred over flexible sigmoidoscopy) beginning at 10-15 years for FAP and every 1-2 years beginning in the late teens for AFAP in those with a small adenoma burden (..."defined somewhat arbitrarily as fewer than 20 adenomas, all less than 1 cm and none with advanced histology...".[4] Other guidelines state to begin colonoscopy screening at 10-12 years in individuals suspected to have FAP and at 18-20 years for individuals suspected to have AFAP and repeat every 1-2 years in both cases.[8] Prophylactic colectomy is generally recommended when sufficient polyps emerge such that polyposis cannot be managed endoscopically.[4] Annual physical examinations are recommended to include thyroid palpation, neurological examination, and abdominal examination.[1] Surveillance may also include upper endoscopy screening, thyroid ultrasounds, imaging for abdominal symptoms suggestive of a desmoid tumor, and screening for hepatoblastomas in children up to five years of age.[4]

Test information

Introduction

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

Known Familial Mutation (KFM) Testing

Known familial mutations 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 single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

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.

Special Considerations

The following special considerations apply to genetic testing for APC.

- Molecular genetic testing of MUTYH should be considered if no APC mutation is found.[1]
- Single gene testing for APC may be completed or multigene panel testing may be performed. Some multigene panels include all polyposis and colorectal cancer genes.[1,4]
- A common variant in the APC gene, called I1307K, may mildly increase the risk for colorectal cancer, but **does not cause FAP**.

Guidelines and evidence

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2015) clinical guidelines stated:[7]

- "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, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndrome."

American Gastroenterological Association

Consensus guidelines from the American Gastroenterological Association (AGA, 2001) recommended:[5,6]

- APC gene testing in individuals age 10 years or older to confirm the diagnosis of FAP or AFAP, or to provide presymptomatic screening in individuals age 10 or older with a first-degree relative with FAP or AFAP.
- First testing an affected family member to establish if a detectable causative variant is present in the family.

American Society of Gastrointestinal Endoscopy

Consensus guidelines from the American Society of Gastrointestinal Endoscopy (ASGE, 2020) recommended:[8]

- "...genetic counseling and testing in patients with clinical polyposis defined as 10 or more adenomas found on a 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 FAP individuals should be tested at ages 10 to 12 years, whereas suspected AFAP and MAP should be tested at ages 18 to 20 years" [low quality]
- "...screening sigmoidoscopy or colonoscopy in children with or suspected to have FAP starting at ages 10 to 12 years [and] follow-up colonoscopy for patients found to have rectosigmoid polyps if sigmoidoscopy was the initial screening test. In patients with negative sigmoidoscopy findings, colonoscopy screening should be offered starting in late teen years" [moderate quality]
- "...surveillance colonoscopy at 1- to 2-year intervals in FAP" [moderate quality]
- "...screening colonoscopy in patients with or suspected to have AFAP starting at ages 18 to 20 years" [low quality]
- "...surveillance colonoscopy at 1- to 2-year intervals in AFAP" [low quality]

National Comprehensive Cancer Network

Evidence- and consensus-based guidelines from the National Comprehensive Cancer Network (NCCN, 2023) stated:[4]

- "APC genetic testing is recommended in a proband to confirm a diagnosis of FAP and allow for pathogenic variant-specific testing in other family members. Additionally, knowing the location of the pathogenic variant in the APC gene can be helpful for predicting severity of polyposis, rectal involvement and desmoid tumors."
- When the family mutation is known, testing for the familial pathogenic APC mutation is recommended for at-risk family members (defined as first-degree relatives or more distant relatives).

- "If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known pathogenic variant in the family."
- "FAP genetic testing in children should be done by age 10-15 y when colon screening would be initiated. If there is intent to do hepatoblastoma screening, FAP genetic testing should be considered in infancy."
- NCCN guidelines provided criteria for adenomatous polyposis testing. These include an individual with one or more of the following: known pathogenic or likely pathogenic variant in APC in the family, at least 20 adenomas (consider testing if ≥10 adenomas), multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE), a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or an individual meeting criteria for serrated polyposis syndrome (SPS) with at least some adenomas.
    - SPS clinical diagnostic criteria are stated as:
        - "≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10mm in size."
        - ">20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum."
        - Note: "The polyp count is cumulative over multiple colonoscopies, and includes any histologic subtype of serrated lesion/polyp"
- These recommendations are Category 2A, defined as "lower-level evidence" with "uniform NCCN consensus."
- Individuals with the APC I1307K mutation should have colonoscopy screening as determined by family history. For individuals not affected by colorectal cancer, colonoscopy screening should occur every 5 years, beginning at age 40 years (or 10 years prior to the age at diagnosis for the affected first-degree relative).

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 familial adenomatous polyposis 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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