Familial Adenomatous Polyposis Testing

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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 Familial Adenomatous Polyposis (FAP)

Definition

FAP is an inherited colorectal cancer syndrome that accounts for up to 1 in 200 colorectal cancers.¹

- 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. The diagnosis is established when a mutation is identified in the adenomatous polyposis coli (APC) gene in an individual with characteristic clinical findings. Polyposis typically begins before age 40. Virtually all people with classic FAP will develop colorectal cancer without intervention. 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 duodenal adenomas and gastric 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.
o FAP with osteomas or soft tissue tumors suggests the Gardner syndrome variant. FAP with medulloblastoma suggests the Turcot syndrome variant.

- Attenuated FAP (AFAP) is a milder form characterized by the presence of 10-99 polyps. Colon cancer generally presents at a later age than classic FAP. Individuals with 100 or more polyps occurring at later ages (35 to 40 years or older) may be found to have AFAP. A personal history of colorectal cancer before age 60 (without polyposis) and a family history of multiple adenomatous polyps may also be seen with AFAP. Currently, there is no consensus regarding precise diagnostic criteria for AFAP.\(^1,2\)

- Almost all cases of FAP are due to mutations in the adenomatous polyposis coli (APC) gene, a tumor suppressor gene. "Fewer than 30% of individuals with AFAP are expected to have an identifiable APC mutation."\(^1\) Most people inherit an APC mutation from an affected parent, but up to 1 in 4 people with FAP have a new mutation with no known affected family members. Parents of someone with FAP may also be unaffected due to germline mosaicism (a mix of normal and mutated copies of the APC gene are confined to the parent's eggs or sperm).\(^1\)

- Management and prevention strategies for those affected with or at-risk for FAP/AFAP include annual flexible sigmoidoscopy or colonoscopy screening beginning at 10-15 years for FAP and every 2-3 years beginning in the late teens for AFAP. Prophylactic colectomy is generally recommended when sufficient polyps emerge such that polyposis cannot be managed endoscopically.\(^3\)

**Test information**

- APC sequence analysis is used to identify disease-causing mutations in those clinically diagnosed with FAP/AFAP.\(^3-6\) Testing may be considered for close relatives of someone with FAP when an affected relative is unavailable for testing.\(^5\)
  - Sequence analysis detects a mutation in up to 90% of individuals clinically diagnosed with FAP.\(^1\) The mutation detection rate is lower for those with AFAP than classic FAP.\(^2\)
  - APC deletion/duplication testing is typically performed in reflex to negative analysis. Deletion/duplication testing detects an additional 8-12% of mutations in those with clinical suspicion of FAP.\(^1\)
  - Molecular genetic testing of MUTYH should be considered next if no APC mutation is found.\(^1\)
  - Single gene testing may be completed or multi-gene testing may be performed. Some multi-gene panels include all polyposis and colorectal cancer genes.\(^1,3\)
  - Once a disease-causing mutation has been identified, at-risk family members can be tested for that known familial mutation. This may be called single site mutation analysis. Those proven not to have inherited a known family mutation through genetic testing can avoid the additional screening required for those at-risk for FAP.\(^1\)
A common variant in the APC gene, called I1307K, may mildly increase the risk for colorectal cancer, but does not cause FAP. Testing for this variant is not widely accepted.

Guidelines and evidence

- Consensus guidelines from the American Gastroenterological Association (AGA, 2001) recommend:
  - APC gene testing in individuals age 10 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 mutation is present in the family.

- Evidence- and consensus-based guidelines from the National Comprehensive Cancer Network (NCCN, 2019) state:
  - "APC genetic testing is recommended in a proband to confirm a diagnosis of FAP and allow for mutation specific testing in family members. Additionally knowing the location of the mutation in the APC gene can be helpful for predicting severity of polyposis, rectal involvement and desmoid tumors."
  - When the family mutation is known, APC gene testing is recommended for at-risk family members (defined as first-degree relatives or more distant relatives if closer relatives are unavailable or unwilling to be tested).
  - When the family mutation is not known, APC gene testing may be considered for first-degree relatives when an affected family member is not available or not willing to test first.
  - "FAP genetic testing should be done by age 10 years when colon screening would be initiated. If there is intent to do hepatoblastoma screening, FAP genetic testing should be considered in infancy."
  - 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 who have a first-degree relative with 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 relative). For individuals not affected by colorectal cancer who do not have a first-degree relative with colorectal cancer, colonoscopy screening should occur every 5 years, beginning at age 40 years.

- Evidence-based guidelines from the American College of Gastroenterology (ACG, 2009) recommend:
“patients with classic FAP (>100 adenomas) should be advised to pursue genetic counseling and genetic testing, if they have siblings or children who could potentially benefit from this testing.” [Grade 2B: “weak recommendation, moderate-quality evidence”].

- The American College of Gastroenterology (ACG, 2015) clinical guidelines state that “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.”

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, AND
- Diagnostic or Predisposition Testing:
  - Family History:
    - 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:
o Personal history:5,7
  ▪ More than 10 cumulative adenomas (known or suspected diagnosis of FAP –
    100 or more adenomas or AFAP – 10 to 100 adenomas), or
  ▪ A desmoid tumor, hepatoblastoma, cribiform-morular variant of papillary
    thyroid cancer, or multifocal/bilateral CHRPE, OR

• Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  o Family history:
    ▪ First degree relative of an individual in whom FAP has been clinically
diagnosed or AFAP is considered (more than 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:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by
    the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous large rearrangement testing, and
  o Previous APC sequencing performed and no mutations found, and
  o No known familial mutation, AND

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

References

   Resource (database online). Copyright University of Washington, Seattle. 1993-

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   Attenuated Familial Adenomatous Polyposis (AFAP) Results from an international

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