Familial Adenomatous Polyposis and MUTYH-Associated Polyposis

AHS-M2024

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Description of Procedure or Service

Familial adenomatous polyposis (FAP) is characterized by development of adenomatous polyps and an increased risk of colorectal cancer (CRC) caused by an autosomal dominant mutation in the APC (Adenomatous Polyposis Coli) gene (Kinzler & Vogelstein, 1996). Depending on the location of the mutation in the APC gene FAP can present as the more severe classic FAP (CFAP) with hundreds to thousands of polyps developing in the teenage years associated with a significantly increased risk of CRC, or attenuated FAP (AFAP) with fewer polyps, developing later in life and less risk of CRC (Brosens, Offerhaus, & Giardiello 2015; Spirio et al., 1993).

MUTYH-associated polyposis (MAP) results from an autosomal recessive mutation of both alleles of the MUTYH gene and is characterized by increased risk of CRC with development of adenomatous polyps. This condition, however, may present without these characteristic polyps (M. L. Nielsen, H., Infante, E., Brand, R., 2015).

Related Policies:
Lynch Syndrome AHS-M2004
Molecular Panel Testing of Cancers to Identify Targeted Therapy AHS-M2109
Genetic Cancer Susceptibility Using Next Generation Sequencing AHS-M2066

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for familial adenomatous polyposis and MUTYH-associated polyposis when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

When Familial Adenomatous Polyposis and MUTYH-Associated Polyposis is covered

Reimbursement is allowed for genetic counseling for individuals being considered for genetic testing for FAP/AFAP and/or MAP.
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Familial adenomatous polyposis and MUTYH-associated polyposis genetic testing is considered medically necessary for the following:

1. Complete sequencing of the APC gene is considered medically necessary for:
   A. Individuals with a personal history of ≥ 10 adenomatous colon polyps, or
   B. Individuals with a personal history of a desmoid tumor, hepatoblastoma or cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE), or
   C. Individuals with a family history of FAP, AFAP, or MAP, and the familial mutation is unknown

2. Duplication/deletion analysis of the APC gene is considered medically necessary when:
   A. Sequencing of the APC gene does not reveal deleterious changes, and the clinical suspicion of FAP remains, or
   B. There is a known familial duplication or deletion

3. Testing for known familial mutations in the APC gene is considered medically necessary for first degree relatives of an individual with known FAP.

4. Testing for the two common MUTYH mutations (Y179C and G396D) is considered medically necessary when:
   A. There is a personal history of ≥ 10 adenomatous colon polyps, or
   B. APC gene testing is negative and high clinical suspicion for FAP/AFAP remains
   C. The individual meets the following criteria for serrated polyposis syndrome (SPS) with at least some adenomas
      i. At least 5 serrated polyps proximal to the sigmoid colon with 2 or more of these being greater than 10 mm; or
      ii. Greater than 20 serrated polyps of any size, but distributed throughout the colon.
      iii. Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
   D. The two common mutations are known familial mutations

5. Sequencing of the MUTYH gene is considered medically necessary when:
   A. Testing for the two common mutations (Y179C and G396D) is negative, or only one common mutation is detected, and the clinical suspicion of MAP remains, OR
   B. Testing is being requested in a member with a known familial mutation in MUTYH. This testing should be limited to the known familial mutation.
   C. Testing is being done in unaffected parent when the other parent has MAP
   D. Unaffected parent is not tested, testing for children is indicated

6. Duplication/deletion analysis of the MUTYH gene is considered medically necessary when:
   A. Sequencing of the MUTYH gene does not detect a mutation, and the clinical suspicion of MAP remains, OR
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B. There is a known familial duplication or deletion.

7. Multi-gene testing is considered **medically necessary** in individuals who meet the APC and MUTYH testing criteria and have no known APC or biallelic mutations.

8. If a pathogenic mutation has been identified in the index patient, predictive testing for the mutation is considered **medically necessary** for the first-degree relatives. In typical FAP, family members that are found to carry the mutation is covered to undergo periodic examination of
   - the recto-sigmoid from the early teens, and
   - the upper gastrointestinal tract from age 25–30 years to monitor adenoma development.

**When Familial Adenomatous Polyposis and MUTYH-Associated Polyposis is not covered**

Familial adenomatous polyposis and MUTYH-associated polyposis is considered **not medically necessary** for the following:

1. Sequencing of the *MUTYH* gene in children is considered **not medically necessary** when one of the parents is unaffected and does not have MUTYH mutation and the other parent has MAP.

2. Multi-gene testing is considered **not medically necessary** in the following situations:
   - An individual is from a family with a known mutation without any other reason for multi-gene testing
   - Multi-gene testing being used as a first-line testing when the family history is strongly suggestive of a known hereditary syndrome.

**Policy Guidelines**

**Scientific Background**

Inherited syndromes that express adenomatous polyps and confer a significantly increased risk of CRC include familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis (MAP) (Jasperson, Tuohy, Neklason, & Burt, 2010). Both FAP and MAP account for less than 1% of all colorectal cancer cases (Chung, 2017; Grover & Stoffel, 2017).

FAP results from mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene. Mutant or absent *APC* results in increased transcription of cell proliferation genes regulated through the Wnt/β-catenin pathway and the earliest malignancies (microadenomas and other small polyps) have lost the second *APC* allele. The *APC* gene is thought to prevent accumulation of β-catenin, and mutations in this gene result in failure of these β-catenin regulatory domains. β-catenin is thought to regulate the proliferation and differentiation of interstitial epithelial cells, and failure of this regulatory mechanism results in cell proliferation. Somatic mutations of this gene are present in 80% of sporadic CRCs and a single germline mutation of this gene is responsible for FAP (Frucht, 2018). The prevalence of FAP is about 1:13,000 (Brosens et al., 2015). More than 300 different mutations have been reported, and the clinical presentation is dependent on the location of the mutation in the *APC* gene (Brosens et al., 2015; Spirio et al., 1993). Mutations in the central part of the gene (Exons 169 to 1393) result in classic FAP characterized by the presence of 100 or more adenomatous colorectal polyps (Chung, 2017). When fully developed, patients can have up to thousands of colorectal adenomas and nearly 100% risk of CRC. About 50% of patients developed adenomas by age 15 and 95% by age 35. If left untreated, FAP patients will develop CRC at an average age of 39 (Brosens et al., 2015). Patients with FAP are also at risk for extracolonic malignancies, such as desmoid tumors, duodenal adenomas, or even brain tumors (Chung, 2017).

In contrast, mutations in either end of the gene predispose to attenuated FAP (AFAP) (Spirio et al., 1993). AFAP is characterized by fewer colorectal adenomas with a later age of onset and an 80% lifetime
risk of CRC compared to FAP. The diagnosis should be considered in patients 40-50 years old with 10-100 adenomas cumulatively. Patients with AFAP are diagnosed about 14 years later on average than classic FAP (44 years of age versus 58 years of age, respectively). Overall, AFAP is a milder, but very similar form, of FAP (Chung, 2017).

*MUTYH*-associated polyposis is caused by biallelic mutations in the *MUTYH* gene base excision repair gene whose protein repairs oxidative damage on the *APC* gene (Sieber et al., 2003). Failure of base excision repair results in transversions in multiple genes, including the *APC* and *KRAS* genes. The two most common mutations in the *MUTYH* gene are Y179C and G396D, but more than 100 unique *MUTYH* gene mutations have been reported. *MUTYH*-associated polyposis is usually characterized by development of between 10 to 100 colorectal polyps by ages 50-60; however, *MUTYH* mutations have been identified in CRC with few or no colorectal polyps. Adenomas are the primary polyp type in patients with *MUTYH*-associated polyposis, but hyperplastic and sessile serrated polyps have been reported in some patients (Grover & Stoffel, 2017). The genes that are mutated strongly influence the polyposis phenotype with the *KRAS* gene mutation resulting in different phenotypes compared to *MUTYH* (Boparai et al., 2008). Furthermore, the genotype of the condition may also make a difference in the clinical presentation. Multiple studies have suggested that the mutation G396D is less severe than the mutation Y179C, with the patients of the G396D genotype tending to develop polyps later and experiencing a later age of onset for those polyps (Guarinos et al., 2014; M. Nielsen et al., 2009).

Although both FAP and *MUTYH*-associated polyposis both cause numerous colorectal adenomas, there are notable differences between the two conditions. Mutations of *MUTYH* typically do not result in FAP. FAP is characterized by mutations in the *APC* gene and may be transmitted from parent to child (although 25% of FAP cases are de novo), whereas *MUTYH*-associated polyposis is not inherited in this manner. Diagnosis of *MUTYH*-associated polyposis requires identification of biallelic pathogenic germline variants of *MUTYH* (Grover & Stoffel, 2017).

A study of 8676 patients who had undergone mutation analysis of the *APC* and *MUTYH* genes was performed by Grover et al. Of these 8676, 7225 had colorectal adenomas. Overall, 1457 patients had classical FAP, and 3253 had AFAP. The study found *APC* mutations in 80% of patients with \( \geq 1000 \) adenomas (95/119), 56% of patients with 100-999 adenomas (756/1338), 10% of patients with 20-99 adenomas (326/3253) and 5% of patients with 10-19 adenomas (50/970). *MUTYH* mutations were found in 2% (2/119), 7% (94/1338), 7% (233/3253), and 4% (37/970) of patients, respectively. The authors concluded that *APC* mutation rate increased as number of adenomas increased, but *MUTYH* mutation rate was relatively constant over all categories. 2098 patients out of 8676 (24%) had a pathogenic *APC* or *MUTYH* mutation, and 6578 (76%) had a non-pathogenic mutation or no mutation in either gene (Grover et al., 2012).

Ciavarella et al investigated genetic causes of unexplained adenomatous polyposis in 8 cases of polyposis with no causative germline variant in *APC* or *MUTYH*. They identified *APC* mosaicism in 50% of patients. In three cases mosaicism was restricted to the colon, while in one it also extended to the duodenum and saliva. One patient without *APC* mosaicism carried an *APC* in-frame deletion of uncertain significance and was found to harbor rare germline variants in *OGG1*, *POLQ*, and *EXO1* genes. The authors concluded that restrictive selection criteria improved the detection of mosaic *APC* patients and that an oligogenic inheritance of rare variants may have a role in sporadic colorectal polyposis (Ciavarella et al., 2018).

Guidelines have been established by several organizations to reduce morbidity and mortality from hereditary forms of polyposis and resulting CRC by identifying individuals at risk and implementing a highly targeted program of cancer surveillance and management guided by the causative mutations identified (Hampel, Bennett, Buchanan, Pearlman, & Wiesner, 2015; Hegde, Ferber, Mao, Samowitz, & Ganguly, 2014; Provenzale et al., 2016; Syngal et al., 2015).

**National Comprehensive Cancer Network (NCCN)**
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The NCCN recommends APC gene testing for individuals with a personal history of ≥20 adenomas and for individuals with a known deleterious familial mutation. The NCCN recommends testing be considered in individuals with a personal history of a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, multifocal/bilateral CHRPE, or 10-20 adenomas (Gupta et al., 2017; NCCN, 2018).

NCCN recommends MUTYH genetic testing for individuals with a personal history of ≥20 adenomas and known deleterious MUTYH mutations in family. The NCCN recommends testing be considered in with a personal history of 10-20 adenomas or individuals meetings criteria for serrated polyposis syndrome with at least some adenomas (NCCN, 2018; Provenzale et al., 2016).

When there is no known familial mutation, NCCN recommends polyposis syndrome specific testing. 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 of the two most common mutations 536A>G and 1187 A>G may be considered before full sequencing if neither mutation is found. When there are known familial mutations in either the APC or MUTYH genes, NCCN recommends testing for those mutations instead of full gene sequencing or multi-gene testing. If a familial mutation is known, genetic testing may be considered for at-risk family members (NCCN, 2018).

Siblings and children of patients with MAP are recommended to have site-specific testing for the familial mutations. Sequencing of MUTYH may be considered in an unaffected parent if one parent has MAP, but if the unaffected parent does not have a MUTYH mutation, genetic testing of children is unnecessary. If the unaffected parent does have a MUTYH mutation, genetic testing of children for MUTYH mutations is “clinically indicated”. A surveillance colonoscopy every 2-3 years is recommended starting at ages 25-30 for at-risk individuals (family member of affected individual or positive test) (NCCN, 2018).

The NCCN guidelines also mention that next generation sequencing (NGS) technology allows for the sequencing of multiple genes associated with a specific family cancer phenotype(s) simultaneously. NCCN lists clinical scenarios for which multi-gene testing “may be considered”, such as adenomatous polyposis (specific to APC, MUTYH, POLE, POLD1), a patient with personal or family history meeting criteria for more than one hereditary cancer syndrome, a colonic polyposis with uncertain histology, second-line testing with inconclusive first-line testing, or if hereditary cancer is suspected. However, the NCCN also recommends against multi-gene testing in the following scenarios: if the mutation is known and there is no other reason for multi-gene testing, if the family history is strongly suggestive of a known hereditary syndrome, or if the CRC has microsatellite instability or MMR protein loss. In these situations, the NCCN states that a syndrome-specific panel may be considered instead (NCCN, 2018).

The NCCN notes that if more than one gene can explain a given cancer syndrome, multi-gene testing may be more efficient and that panels that include highly penetrant genes of CRC may be cost-effective. For patients testing negative for a certain syndrome, panel testing may be an option if the personal and family histories are “strongly suggestive” of an inherited condition. Finally, the NCCN recommends genetic counseling before and after genetic testing is done (NCCN, 2018).

NCCN recommendations follow the American Society Clinical Oncology (ASCO), which issued an updated statement regarding genetic testing in 2015. ASCO states that informed consent, as well as the possibility of discovery of unexpected and harmful mutations, should be communicated carefully to the patient. ASCO states that genetic counseling is imperative both before and after genetic testing, as many genes have uncertain clinical utility and a specialist may help provide informed clinical decision-making (NCCN, 2018; Robson et al., 2015).

American College of Medical Genetics and Genomics (ACMG, 2014)
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ACMG recommends testing for FAP in individuals with “100 ≤ polyps with autosomal dominant inheritance, and for at-risk family members of individuals with known familial mutations”. The ACMG also recommends testing for FAP in individuals with conditions such as congenital hypertrophy of retinal pigment epithelium or osteomas. It also recommended that “FAP testing be performed using full sequencing of the \(APC\) gene. If no mutation is detected, then testing for large gene rearrangements should be performed (Hegde et al., 2014).” The ACMG notes that mutations are detected in 80% of patients with FAP with DNA sequencing detecting 87% of smaller mutations, such as deletions or point mutations. The remaining mutations are larger mutations, such as gross duplications, which can be detected by RT-PCR or MLPA. ACMG recommends considering testing for AFAP in individuals with <100 adenomas. They note that individuals with 100 or more polyps at 35-40 years or older may be found to have AFAP. According to ACMG, frequent right-sided distribution of polyps is usually noted in these individuals and adenomas and cancers at an age older than that for classic FAP and other GI manifestations are found (Hegde et al., 2014).

ACMG recommends \(MUTYH\) gene testing for individuals with colorectal cancer diagnosed at less than 40, the presence of 10 or more adenomatous polyps without \(APC\) gene mutation, and a family history of colon cancer with an autosomal recessive inheritance including colon cancers with or without polyps (Hegde et al., 2014). ACMG indicates that \(MUTYH\) testing should begin with testing for the two common mutations p.Y165C and p.G382D, and if none or one mutation is identified, then full sequencing of the \(MUTYH\) gene should be considered. The ACMG notes that 80% of mutations in Caucasian and North European populations are of these two variants, but sequencing of the entire gene may detect up to 99% of mutations. The ACMG also recommends that testing of the \(MUTYH\) gene should also be offered to at-risk family members. Sanger sequencing and NGS are both recommended methods for sequencing. Finally, if heterozygosity for only one common mutation is detected, or no mutation is detected at all, then sequencing of the entire \(MUTYH\) gene may be considered (Hegde et al., 2014).

**ACMG and the National Society of Genetic Counselors (NSGC, 2015)**

ACMG and NSGC recommend that referral for genetic counseling should be considered for “any individual with a personal history of or first-degree relative with a total of ≥10 adenomatous colon polyps with or without a colorectal or other FAP-associated cancer, a cribriform morular variant of papillary thyroid cancer; a desmoid tumor; or hepatoblastoma diagnosed before age 5” (Hampel et al., 2015).

**European Society for Medical Oncology (ESMO, 2013)**

ESMO recommends germline testing of \(APC\) and \(MUTYH\) for patients with 10 or more colorectal adenomas. Full germline testing should include DNA sequencing and large rearrangement analysis. Testing for \(MUTYH\) may start with the two most common mutations (Y179C, G396D), followed by analysis of the entire gene in heterozygotes. Founder mutations present in certain ethnic groups should also be taken into account. If a mutation is detected, testing may also be offered to at-risk family members (Balmaña, Balaguer, Cervantes, Arnold, & ESMO, 2013).

**American Society of Colon and Rectal Surgeons (ASCRS, 2017)**

The ASCRS has released guidelines on inherited polyposis syndromes. A polyposis diagnosis should be considered “in patients with over 20 adenomas, patients with history of desmoid tumor, extracolonic manifestations, or family members of individuals with known FAP, AFAP, or MAP”. Germline testing of the \(APC\) gene is recommended for these individuals. The ASCRS lists 20 as the cutoff as the risk of finding a genetic mutation rises above 10% at this mark. Genetic counseling is recommended prior to
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genetic testing. The ASCRS recommends patients with clinical polyposis but without an identified mutation to be treated according to their phenotype. However, this was noted to be a weak recommendation based on low quality evidence (Herzig et al., 2017).

American College of Gastroenterology (ACG)

The ACG recommends 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 (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”(Syngal et al., 2015).

ACG further states “failure to identify a mutation in an index case does not rule out the diagnosis of adenomatous polyposis, as mutations cannot be found in all families. If testing is negative, and clinical suspicion remains high, testing for other possible underlying genes should be considered. Failure to find a mutation means that all close relatives must still be screened as if they have FAP. Finding a mutation confirms the diagnosis of adenomatous polyposis and allows relatives to be tested with a high degree of accuracy. Once an affected patient has been genotyped, all at-risk relatives can be screened for the mutation”(Syngal et al., 2015).

State and Federal Regulations, as applicable

A search for “APC” on January 2, 2019 did not yield any results, but widely used mutation analysis techniques are well-established and well-validated. On January 18, 2019, the FDA approved the MUTYH-Associated Polyposis (MAP) testing by 23andMe, Inc. (FDA, 2019).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81201, 81202, 81203, 81406, 96040, S0265

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 5/2019

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019

Policy Implementation/Update Information

1/1/2019  New policy developed. BCBSNC will provide coverage for familial adenomatous polyposis and MUTYH-associated polyposis when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019 for effective date 4/1/2019. (lpr)

5/14/19  Reviewed by Avalon 1st Quarter 2019 CAB. Updated Description and Policy Guidelines sections. Added Related Policies and State/Federal Guidelines sections. No change to policy intent. Medical Director review 5/2019. (lpr)

10/1/19  Specialty Matched Consultant Advisory Panel review 8/21/2019. No change to policy statement. Deleted coding table from Billing/Coding section. Medical Director review 8/2019. (lpr)

10/29/19  Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

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subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.