

Corporate Medical Policy

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). Two other subtypes of FAP include Gardner syndrome, which causes non-cancer tumors of the skin, soft tissues, and bones, and Turcot syndrome, a rare inherited condition in which individuals have a higher risk of adenomatous polyps and colorectal cancer. In classic FAP, the most common type, patients usually develop cancer in one or more polyps as early as age 20, and almost all classic FAP patients have CRC by the age of 40 if their colon has not been removed (American_Cancer_Society, 2020).

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.

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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.

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. There is a personal history of multifocal/bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE), or
 - C. APC gene testing is negative and high clinical suspicion for FAP/AFAP remains
 - D. 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
 - E. 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.

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- 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
 - 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, 2020; Grover & Stoffel, 2020).

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, 2020). 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, 2020). 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

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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, 2020).

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, 2020). 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, 2020).

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 ≥ 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 *OGGI*, *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,

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Bennett, Buchanan, Pearlman, & Wiesner, 2015; Hegde, Ferber, Mao, Samowitz, & Ganguly, 2014; Provenzale et al., 2016; Syngal et al., 2015).

In a study by Yang et al. (2020), next-generation sequencing (NGS) panel, multiplex ligation-dependent probe amplification (MLPA), whole-exome sequencing (WES), and Sanger sequencing were used to determine a diagnostic method for variant-negative FAP patients. Although definite pathogenic variants of the *APC* gene are identified in the majority of FAP patients, there are still numerous variant-negative patients. NGS and MLPA did not identify any variants of the *APC* gene; however, WES recognized three patients with a point variant (c.-190G>A) in the noncoding region of the *APC* gene. Sanger sequencing identified a variant carrier during screening of the family. This study showed that the c.-190G>A variant can cause classic FAP but can be missed by conventional genetic testing. Therefore, "utilizing sequencing technologies covering a larger area can help us to further explore the pathogenesis in variant-negative FAP cases" (M. Yang et al., 2020).

Peutz-Jeghers Syndrome (PJS)

PJS is another uncommon polyposis syndrome that occurs 1 in 8,300 to 1 in 20,000 births (Giardiello & Trimpath, 2006). This condition is characterized by two clinical signs: pigmented mucocutaneous macules (melanin spots) and multiple hamartomatous gastrointestinal polyps. Those affected are at higher risk for both gastrointestinal and extra-intestinal cancers. Pathogenic mutations in the *STK11* gene is most strongly associated with PJS; although not every genetic mutation associated with PJS has been identified (D. C. Chung, 2020a).

Over 95% of PJS patients present with mucocutaneous macules, which are typically found on the lips or around the lips, palms, soles of the feet, or on the buccal mucosa. However, these macules tend to be most prevalent in the first two years and typically fade after puberty. Most patients will also present with hamartomatous polyps, typically developing in the first decade of life. These polyps do not have any particularly distinguishing features and may be indicative of several other syndromes, such as Cowden syndrome (D. C. Chung, 2020b).

Jia et al. analyzed clinical features of 46 patients with Peutz-Jeghers syndrome (PJS). The authors identified "black spots, abdominal pain, hematochezia, and anemia" as the main clinical features. Histologically, "20 patients were classified as hamartomatous polyps, 18 as adenomatous polyps, 14 as inflammatory polyps, and 10 as zigzag polyps". 11 patients underwent gene sequencing with a panel of 20 genes, and 5 were found to have gene mutations. 3 of these patients were found to have mutations in the *STK11* gene (Jia, Fu, Li, Kang, & Sheng, 2018).

In a study by Wu et al. (2020), direct sequencing using the QIAamp DNA Blood Mini Kit and multiplex ligation-dependent probe amplification (MLPA) tests were used to detect germline *STK11* mutations in 38 patients clinically diagnosed with Peutz-Jeghers syndrome and their healthy relatives. RNA sequencing was performed in polyps of PJS patient and control groups to evaluate the difference of *STK11* expression. A clinical PJS diagnosis was made when an individual had two of the following: two or more histologically confirmed Peutz-Jeghers-type hamartomatous polyps, mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers, and family history of PJS. Germline mutation screening of the *STK11* gene detected a pathogenic variant in all probands with a 100% mutation detection rate. "Twenty variants were nucleotide substitutions or indels that were detected by Sanger sequencing (7 were missense variants, and 13 variants were truncating). All mutations fell within the coding region spanning exon 1 and exon 8, and no mutation in exon 9 was identified in any of these PJS individuals" (Wu et al., 2020). While missense mutations did not influence *STK11* expression, truncated mutations resulted in lower *STK11* expression which may cause greater damage to the gene product and a more severe PJS phenotype. In this study, the 13 patients with a truncated *STK11* variant did have earlier onset for PJS symptoms, including intestinal obstruction and first operation events, than those with missense mutations. This indicates that patients with truncated variant need earlier management to prevent complications. In addition, this study identified a fetus with a *STK11* pathogenic variant through non-invasive prenatal testing (NIPT). The parents chose to give birth to this fetus, and melanin spots appeared on the lips at approximately

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1 year old and have gradually increased. This indicates that there are broad application prospects for prenatal testing and preimplantation genetic diagnosis. Due to the significance of genetic testing in this study, the author states that "it is important to detect *STK11* gene mutations to make early diagnoses and treatments to reduce the occurrence of GI complications and malignancies" (Wu et al., 2020).

Juvenile Polyposis Syndrome (JPS)

JPS is another condition thought to confer additional risk for colorectal and gastric cancer. JPS is caused by variants in the *BMPRIA* or *SMAD4* genes, but no genetic variant is found in 20-30% of the cases. These genes code for a protein that play a role in the TGF β signal transduction system. In patients with *SMAD4* gene variant, severe polyposis in the stomach or duodenum is highly likely (NHS, 2019). Similarly to syndromes discussed above, this condition is characterized by numerous polyps in the GI tract. More than half of affected JPS patients will present with rectal bleeding and will be symptomatic by 20 years old. Differentiating JPS from other hamartomatous syndromes can be difficult, but patients meeting the clinical diagnosis criteria for JPS will often undergo genetic testing for the *BMPRIA* and *SMAD4* genes (D. C. Chung, 2020a).

Gonzalez et al. evaluated the clinicopathological features of 22 patients with "abundant gastric juvenile-type or hyperplastic-like polyps". 14 of these patients were diagnosed with JPS, and these diagnoses were diagnosed at an average of 40 years. 18 of the 22 cases showed "complete or near-complete carpeting of the gastric mucosa by innumerable polyps", and *SMAD4* immunohistochemical staining revealed "patchy loss" in polyps in 19 of 20 tested cases. Furthermore, 5 of 6 patients tested harbored a *SMAD4* mutation (Gonzalez et al., 2017).

National Comprehensive Cancer Network (NCCN, 2020a)

The NCCN recommends APC or MUTYH gene testing for individuals with a personal history of ≥ 20 adenomas and for individuals with a known deleterious familial mutation, and individuals with multifocal or bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE). The NCCN recommends testing be considered in individuals with a personal history of a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, unilateral CHRPE, multifocal/bilateral CHRPE, or 10-20 adenomas (Gupta et al., 2017; NCCN, 2020b). If an APC gene mutation is found, an annual colonoscopy or flexible sigmoidoscopy starting at 10-15 years of age is recommended.

If a patient has a personal or family history of a known pathogenic variant of a colorectal polyposis or cancer gene, further evaluation is warranted. When there is no known familial or personal mutation, the NCCN recommends determining the patient's history of the following clinical signs:

- >10 adenomatous polyps
- ≥ 2 hamartomatous polyps
- ≥ 5 serrated polyps proximal to the sigmoid colon

If any of these features are identified, the NCCN recommends a detailed risk assessment and "potential" genetic evaluation to rule out polyposis syndromes. The NCCN also recommends within the algorithm concerning risk assessment/genetic evaluation for possible polyposis syndromes that for individuals for more than 10 adenomas to test for FAP, AFAP, MAP, and rare genetic causes of multiple adenomatous polyps. Within this latter group, the genes associated "include, but are not limited to monoallelic pathogenic variants in *GREM1*, *POLE*, *POLD1*, *AXIN2*, and biallelic pathogenic variants in *NTHL1* and *MSH3*."

The NCCN also notes the following: "When colonic polyposis is present only in siblings, consider recessive inheritance. For example MAP follows a recessive pattern of inheritance, so *MUTYH* testing can be performed prior to *APC* if a recessive pattern is apparent in the pedigree...*MUTYH* genetic testing is not

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indicated based solely on a personal history of a desmoid tumor, hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer...” (NCCN, 2020b).

The NCCN also makes this note for siblings of a patient with MAP: they are recommended to have site-specific testing for the familial pathogenic mutations. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to have one *MUTYH* pathogenic variant, testing the children for the familial *MUTYH* pathogenic variants is indicated. If the unaffected parent is not tested, comprehensive testing of *MUTYH* should be considered in the children. Testing for children of *MUTYH* heterozygotes should be offered if the other parent is also a heterozygote or could still be offered if the other parent is not a heterozygote and management would change (if they have an FDR [first-degree relative] affected with CRC) or inform reproductive risks (since their future children could be at-risk for MAP) (NCCN, 2020b).

The NCCN notes that a classical diagnosis of FAP is suspected when there are greater than 100 polyps present at a young age; however, genetic testing with multi-gene panel is recommended to differentiate between FAP, AFAP, MAP polyposis due to a mutation in a rare gene for which testing is available, and colonic polyposis of unknown etiology (NCCN, 2020b).

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, 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, if family cancer history does not meet established testing guidelines, or if an individual with limited or unknown family history is concerned about cancer predisposition. 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 or if genetic testing is performed as first-line testing with a family history that is strongly suggestive of a known hereditary syndrome. In these situations, the NCCN states that a syndrome-specific panel may be considered instead. Overall, the NCCN states that multi-gene panels that include genes associated with Lynch Syndrome and other colorectal genes of high penetrance may be cost-effective. Panel testing may be an option if the personal and family histories are “strongly suggestive” of an inherited condition. The NCCN also recommends genetic counseling before and after genetic testing is done (NCCN, 2020b).

The NCCN recommends genetic testing for juvenile polyposis syndrome patients, noting that 50% of cases occur due to pathogenic *SMAD4* or *BMPRIA* mutations. If there is a known familial mutation of *SMAD4*, genetic testing should be performed within the first 6 months of life. The NCCN also remarks that the majority of Peutz-Jeghers Syndrome cases occur due to pathogenic variants in the *STK11/LKB1* gene (NCCN, 2020b).

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, 2020b; Robson et al., 2015).

The NCCN also notes several genes that may decide treatment. For patients with pathogenic variants in *GREM1*, *POLD1*, *POLE*, *AXIN2*, *NTHL1*, and *MSH3*, they recommend beginning a colonoscopy at 25-30 years old and performing one every 2-3 years if negative. If polyps are found, a colonoscopy should be performed every 1-2 years, with surgical evaluation as needed. However, the NCCN does note that recommendations for these genes are still “evolving” at this time and that caution is needed when determining surveillance regimes.

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).

The guidelines also list clinical symptoms that should warrant assessment for cancer predisposition for JPS and PJS. For JPS, they note the following symptoms:

- “3-5 cumulative histologically proven juvenile polyps in the same person”
- “Multiple juvenile polyps throughout the GI tract in the same person”
- “Any number of juvenile polyps with a family history positive of JPS”

For PJS:

- “≥2 cumulative histologically proven PJ polyps in the same person”
- “≥1 PJ polyp and mucocutaneous hyperpigmentation in the same person”
- “Any number of PJ polyps and a positive family history of PJS” (Hampel et al., 2015).

European Society for Medical Oncology (ESMO) (Balmaña, Balaguer, Cervantes, Arnold, & ESMO, 2013; Stjepanovic et al., 2019)

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ESMO published a 2019 update for hereditary gastrointestinal cancers, including some polyposis syndromes. These recommendations are as follows:

- For FAP, “Patients with multiple colorectal adenomas (>10) should be considered for panel germline genetic testing that includes *APC*, *MUTYH*, *POLE*, *POLD1* and *NTHL1* genes. *APC* analysis should include large rearrangements”
- “Biallelic *MUTYH* mutations should be suspected in cases of AFAP or FAP with a recessive pattern of inheritance, diagnosis before the age of 50 years, and multiple colonic polyps”
- “A multigene single analysis of *APC*, *MUTYH* (all exons), *POLE*, *POLD1* and *NTHL1* is recommended”
- For *POLE*-and *POLD1*- mutation-positive PPAP and *NTHL1*-mutation-positive adenomatous polyposis, colonoscopic surveillance should follow MAP recommendations” (Stjepanovic et al., 2019).

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 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).

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Polyposis Working Group (Latchford et al., 2019)

This working group released guidelines on both Juvenile Polyposis Syndrome (JPS) and Peutz-Jeghers Syndrome (PJS).

For JPS, the Working Group recommends routine predictive testing for at-risk children at 12-15 years of age. If a child has rectal bleeding before this age, a colonoscopy should be performed, and if polyps are found, that child should undergo genetic testing.

Pediatric patients with a *SMAD4* mutation should be evaluated for Hereditary Hemorrhagic Telangiectasia (HHT), including screening for cerebral and pulmonary arteriovenous malformations.

“Children with *BMPRIA* mutation and early onset polyposis and/or a severe phenotype and/or extraintestinal manifestations should be evaluated for *PTEN* mutation”.

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“If a specific gene mutation has been detected in a child, then genetic testing should be offered to all first-degree family members. If no specific gene mutation was detected, then first-degree relatives should be referred for screening colonoscopy at the age of 12 to 15 years” (Cohen et al., 2019).

For PJS, ESPGHAN recommends offering predictive genetic testing for an asymptomatic at-risk child as early as 3 years of age. Symptomatic at-risk children should have genetic testing performed earlier.

However, the ESPGHAN notes that “No clear genotype-phenotype correlation has been demonstrated in PJS. Furthermore there have been no clear clinical differences found between cases with and without detectable germline *STK11* mutations” (Latchford et al., 2019).

American Society for Gastrointestinal Endoscopy (ASGE) (J. Yang et al., 2020)

ASGE released recommendations for the role of genetic testing in the management of patients with FAP syndromes. As family history may not be present due to germline mutations of the *APC* gene, ASGE recommends genetic testing to make a confirmatory FAP diagnosis before moving forward with morbid surgery or invasive endoscopic screening. Genetic testing is also recommended when a patient presents with ten or more cumulative adenomatous polyps on a single colonoscopy, if a patient presents with ten or more adenomas and a history of CRC, or if a patient has twenty or more adenomatous polyps in a lifetime. In addition, genetic counseling is recommended for all patients with or suspected to have FAP syndromes and first-degree relatives (J. Yang et al., 2020).

APC gene testing is recommended in children at the age of 10-12 years. If AFAP or MAP is suspected, patients should undergo genetic testing at the age of 18-20 years. Younger children, aged 6 months to 5 years, can undergo confirmatory *APC* gene testing if parents agree to screen for hepatoblastoma with alpha-fetoprotein test and liver function test every 6 months. Otherwise, testing is deferred until 10-12 years old. Children without *APC* gene abnormalities should follow average-risk screening guidelines (J. Yang et al., 2020).

Finally, the guideline comments that “Once an individual is found to be affected with MAP, his or her relatives should also be screened for mutations in *MUTYH*...Similar to FAP, genetic testing for mutations in *MUTYH* should be considered in those with (1) 20 or more colorectal adenomas over multiple colonoscopies, (2) a known family history of MAP, (3) 10 or more adenomas found on a single colonoscopy, or (4) criteria for serrated polyposis syndrome with at least some adenomas noted on examination”. The guideline further notes “serrated polyposis syndrome” is defined by the WHO as one of the following conditions: “(1) at least 5 serrated polyps proximal to the sigmoid colon with 2 or more >10 mm in size, (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis syndrome, or (3) >20 serrated polyps of any size distributed throughout the colon.” The guideline does remark that genetic testing for *MUTYH* in children should be postponed until adulthood due to the later onset of the condition.

American Gastrointestinal Association (AGA) (Boardman, Vilar, You, & Samadder, 2020)

AGA released recommendations on genetic testing for young adult-onset colorectal cancer. AGA recommends genetic testing to all young adult CRC patients based on the patient’s family history of hereditary CRC, other cancer syndromes, and the presence of polyps. AGA also recommends germline testing for those who do not fit clinical criteria for one hereditary syndrome or have no family history of cancer. AGA encourages early integration of genetic counselors as increased genetic testing could lead to the chances of finding genetic variants of unknown significance or a pathogenic variant that does not have clear management guidelines (Boardman et al., 2020).

American College of Gastroenterology (ACG)

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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).

ACG also notes that “Individuals with perioral or buccal pigmentation and/or two or more histologically characteristic GI hamartomatous polyp(s) or a family history of PJS should be evaluated for PJS.” Further, they state that genetic evaluation of a patient with “possible” PJS should include testing for *STK11* mutations. Regarding JPS, ACG recommends that “Individuals with five or more juvenile polyps in the colorectum or any juvenile polyps in other parts of the GI tract should undergo evaluation for JPS.” A genetic evaluation of a patient with “possible” JPS should include testing for *SMAD4* and *BMPRIA* mutations (Syngal et al., 2015).

State and Federal Regulations, as applicable

A search for “APC”, “*STK11*”, “*SMAD4*”, and “*BMPRIA*” on January 21, 2021 did not yield any relevant 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, 2020).

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, 81404, 81405, 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

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Specialty Matched Consultant Advisory Panel 8/2020

Medical Director review 4/2021

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. Policy noticed 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)

- 9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)

- 5/4/21 Reviewed by Avalon 1st Quarter 2021 CAB. Medical Director review 4/2021. Under “When Covered” section item b. added: “there is a personal history of multifocal/bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE). Updated Policy Guidelines and references. (lpr)

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