Genetic Testing for Polyposis Syndromes

Policy Number: AHS – M2024 – Genetic Testing for Polyposis Syndromes

Prior Policy Name and Number, as applicable:
- AHS – M2024 – Familial Adenomatous Polyposis and MUTYH-Associated Polyposis

Initial Presentation Date: 07/01/2021
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I. Policy Description

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 (FAP) with hundreds to thousands of polyps developing starting in the teenage years associated with a significantly increased risk of CRC, or attenuated FAP (AFAP) with fewer polyps, developing later in life with lower 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).

Two other polyposis syndromes are Juvenile Polyposis Syndrome (JPS) and Peutz-Jeghers Syndrome (PJS). These syndromes are characterized by polyps in the GI tract and are often associated with SMAD4 or BMPR1A mutations and STK11 mutations, respectively (D. C. Chung, 2019a, 2019b).

II. Related Policies

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III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

1. Genetic counseling MEETS COVERAGE CRITERIA for individuals being considered for genetic testing for Polyposis Syndromes.

2. Complete sequencing of the APC gene MEETS COVERAGE CRITERIA for:
   a. Individuals with a personal history of \( \geq 10 \) adenomatous colon polyps, or
   b. Individuals with a personal history of a desmoid tumor, hepatoblastoma or cribriformmorular 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

3. Duplication/deletion analysis of the APC gene MEETS COVERAGE CRITERIA 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

4. Testing for known familial mutations in the APC gene MEETS COVERAGE CRITERIA for first degree relatives of an individual with known FAP.

5. Testing for the two common MUTYH mutations (Y179C and G396D) MEETS COVERAGE CRITERIA when
   a. There is a personal history of \( \geq 10 \) adenomatous colon polyps, or
b. *APC* gene testing is negative and high clinical suspicion for FAP/AFAP remains, or

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, or

   iii. Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis

6. Sequencing of the *MUTYH* gene **MEETS COVERAGE CRITERIA** 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

7. Duplication/deletion analysis of the *MUTYH* gene **MEETS COVERAGE CRITERIA** 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.

8. Multi-gene testing **MEETS COVERAGE CRITERIA** in individuals who meet the *APC* and *MUTYH* testing criteria and have no known *APC* or biallelic mutations.

9. If a pathogenic mutation has been identified in the index patient, predictive testing for the mutation **MEETS COVERAGE CRITERIA** for the first-degree relatives. In typical FAP, family members that are found to carry the mutation is covered to undergo periodic examination of

   a. The recto-sigmoid from the early teens, and

   b. The upper gastrointestinal tract from age 25–30 years to monitor adenoma development.

10. Genetic testing of *SMAD4* and *BMPR1A** MEETS COVERAGE CRITERIA** for:
a. Individuals with a known family history of JPS, SMAD4, or BMPR1A mutation; or
b. Individuals with at least three juvenile polyps in the colorectum; or
c. Individuals with any number of juvenile polyps in other regions of the GI tract

11. Genetic testing of STK11/LKB1 MEETS COVERAGE CRITERIA for:
   a. Individuals with a known family history of Peutz-Jeghers Syndrome or STK11/LKB1 mutation; or
   b. Individuals with perioral, buccal, or mucocutaneous hyperpigmentation and at least one histologically characteristic GI hamartomatous (PJ) polyp; or
   c. Individuals with two or more cumulative histologically proven PJ polyps

12. For individuals with more than 10 colorectal adenomas, genetic testing of GREM1, POLE, POLD1, AXIN2, NTHL1, and MSH3 MEETS COVERAGE CRITERIA.

13. Sequencing of the MUTYH gene in children DOES NOT MEET COVERAGE CRITERIA when one of the parents is unaffected and does not have MUTYH mutation and the other parent has MAP.

14. Multi-gene testing DOES NOT MEET COVERAGE CRITERIA in the following situations:
   a. An individual is from a family with a known mutation without any other reason for multigene testing
   b. Multi-gene testing being used as a first-line testing when the family history is strongly suggestive of a known hereditary syndrome

IV. Scientific Background

*Familial Adenomatous Polyposis (FAP) and MUTYH-Associated Polyposis (MAP)*

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 (D. Chung, 2019; Grover & Stoffel, 2018).

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 intestinal 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, 2017; D. Chung, 2019). 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 (D. Chung, 2019).

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 (D. Chung, 2019).

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, 2018). 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, 2018).

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 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).

**Peutz-Jeghers Syndrome (PJS)**

PJS is another uncommon polyposis syndrome. 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, 2019b).

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, 2019b).

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).

**Juvenile Polyposis Syndrome (JPS)**

JPS is another condition thought to confer additional risk for colorectal and gastric cancer. Similarly to syndromes discussed above, this condition is characterized by numerous polyps in the GI tract. More
than half of affected 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 \textit{BMPR1A} and \textit{SMAD4} genes (D. C. Chung, 2019a).

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 nearcomplete carpeting of the gastric mucosa by innumerable polyps”, and \textit{SMAD4} immunohistochemical staining revealed “patchy loss” in polyps in 19 of 20 tested cases. Furthermore, 5 of 6 patients tested harbored a \textit{SMAD4} mutation (Gonzalez et al., 2017).

V. \textbf{Guidelines and Recommendations}

\textit{National Comprehensive Cancer Network (NCCN, 2019)}

The NCCN recommends \textit{APC} or \textit{MUTYH} gene testing for individuals with a personal history of \textit{>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 11-20 adenomas (Gupta et al., 2017; NCCN, 2019). If an \textit{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:

- \textit{>10} adenomatous polyps
- \textit{≥2} hamartomatous polyps
- \textit{≥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 mutations in \textit{GREM1, POLE, POLD1, AXIN2}, and biallelic mutations in \textit{NTHL1} and \textit{MSH3}.”

The NCCN also notes the following: “When colonic polyposis is present in a single person with a negative family history, consider testing for a de novo \textit{APC} mutation; if negative, follow with testing of \textit{MUTYH}. Targeted testing of the two most common mutations 536A>G and 1187 A>G may be considered first followed by full sequencing if biallelic pathogenic variants are not found. When
colonic polyposis is present only in siblings, consider recessive inheritance and test for MUTYH first. Order of testing for APC and MUTYH is at the discretion of clinician. MUTYH genetic testing is not indicated based on personal history of a hepatoblastoma cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral CHRPE (NCCN, 2019).

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, 2019).

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, 2019).

The NCCN recommends genetic testing for juvenile polyposis syndrome patients, noting that 50% of cases occur due to pathogenic SMAD4 or BMP14 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, 2019).

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, 2019; 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 Gastroenterology (ACG, 2015)

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). The ACG recommends screening for CRC in patients with or at risk for “classic AP syndromes” by annual colonoscopy or flexible sigmoidoscopy starting at puberty. The ACG also recommends surveillance by colonoscopy in families with AFAP or MAP (Syngal et al., 2015).

ACG further states that failure to identify a mutation does not rule out the diagnosis of adenomatous polyposis. Testing for any possible underlying genes should be considered if clinical suspicion is high. Failure to find a mutation means that all close relatives must still be screened, but finding a mutation confirms the diagnosis and allows relatives to be tested accurately. Once an affected patient has been genotyped, all at-risk relatives can be screened properly (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 *BMPR1A* mutations (Syngal et al., 2015).

American College of Medical Genetics and Genomics (ACMG, 2014)

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”.

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)**

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).
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 BMPR1A mutation and early onset polyposis and/or a severe phenotype and/or extraintestinal manifestations should be evaluated for PTEN mutation”.

“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).

VI. State and Federal Regulations, as applicable

A search for “APC”, “STK11”, “SMAD4”, and “BMPR1A” on January 31, 2020 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.

VII. Applicable CPT/HCPCS Procedure Codes

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</tr>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 610 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
</tbody>
</table>
| 81406  | Molecular pathology procedure, Level 7  
**Gene:**  
*MUTYH* (mutY homolog [E.coli]) (eg, MYH-associated polyposis), full gene sequence |
| 81479  | Unlisted molecular pathology procedure |
| 96040  | Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family |
| S0265  | Genetic counseling, under physician supervision, each 15 minutes |


*Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*
VIII. Evidence-based Scientific References


