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Genetic Testing for Polyposis Syndromes

Policy Number:	Prior Policy Name and Number:
AHS – M2024	Not applicable
Initial Effective Date:	**Current Effective Date:**
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Line(s) of Business:	**Precertification:**
HMO; PPO; QUEST Integration; Medicare; FEP	Refer to the GTM Utilization Review Matrix

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, affecting one in 8,000-18,000 individuals in the United States.[1-3] Depending on the location of the mutation in the *APC* gene, FAP can present as the more severe classic FAP with hundreds to thousands of polyps developing at the ages of 10-12 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.[4,5] 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.[6]

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.[7]

There are two other polyposis syndromes known as 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.[8,9]

II. Related Policies

Policy Number	Policy Title
AHS-M2004	Lynch Syndrome
AHS-M2026	Testing for Colorectal Cancer Management
AHS-M2179	Prenatal Screening (Genetic)

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. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) Genetic counseling **IS REQUIRED** for individuals being considered for genetic testing for polyposis syndromes.

2) For individuals (see Note 1) in a family with a ~~pathogenic~~ familial pathogenic/likely pathogenic (P/LP) polyposis gene variant, the following testing **MEETS COVERAGE CRITERIA**:

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a) Testing restricted to the known ~~pathogenic~~ familial P/LP variant.

b) Comprehensive genetic testing, including muti-gene panel testing (see Note 2), when the specific familial ~~mutation~~P/LP variant is unknown.

3) For individuals (see Note 1) who have no known familial ~~pathogenic~~P/LP variant(s), multi-gene panel testing (see Note 2, Note 3) for polyposis syndrome risk factors **MEETS COVERAGE CRITERIA** in **any** of the following situations:

a) For individuals with a personal history of ~~multiple polyps in the gastrointestinal tract~~**any** of the following:

i) Ten or more cumulative adenomatous polyps.

~~ii) Two or more hamartomatous polyps.~~

~~iii) Five or more serrated polyps.~~

~~b) For individuals with a personal history of **any** of the following:~~

ii) Multifocal/bilateral or unilateral congenital hypertrophy of retinal pigment epithelium (CHRPE).

iii) Cribriform-morular variant of papillary thyroid cancer.

~~iv) Primary brain tumor (e.g., medulloblastoma).~~

iv) Desmoid tumor.

~~ii)~~v) Hepatoblastoma.

~~vi) Osteomas.~~

~~vii) Supernumerary teeth.~~

b) For individuals who meet criteria for serrated polyposis syndrome (see Note 4) with at least some of the qualifying polyps being adenomas.

c) For individuals who were diagnosed with any cancer before 30 years of age and for whom an APC P/LP variant was found on tumor-only genomic testing.

4) In an unaffected reproductive partner of an individual with *MUTYH*-associated polyposis (MAP), comprehensive sequencing of *MUTYH* **MEETS COVERAGE CRITERIA.**

5) Genetic testing of *SMAD4* and *BMPR1A* **MEETS COVERAGE CRITERIA** in any of the following situations:

a) For individuals with a known family history of juvenile polyposis syndrome (JPS) or a known ~~pathogenic~~ familial P/LP *SMAD4* or *BMPR1A* ~~mutations~~variant (testing restricted to the known ~~pathogenic~~ familial ~~mutation~~P/LP variant).

b) For individuals with at least five juvenile polyps in the colorectum.

c) For individuals with juvenile polyps in more than one organ of the GI tract.

d) For individuals for whom a *BMPR1A* or *SMAD4* P/LP variant was detected on any tumor type by tumor genomic profiling in the absence of germline mutation testing.

6) Genetic testing of *STK11* (formerly known as *LKB1*) **MEETS COVERAGE CRITERIA** in any of the following situations:

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a) For individuals with a known family history of Peutz-Jeghers syndrome (PJS) or a known ~~pathogenic~~ familial P/LP *STK11* ~~mutation~~variant (testing restricted to the known ~~pathogenic~~ familial ~~mutation~~P/LP variant).

b) For individuals with mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers and who have any number of PJS polyps.

c) For individuals with two or more histologically proven ~~Peutz-Jeghers-type~~PJS-type hamartomatous polyps of the GI tract.

d) For individuals for whom an *STK11* P/LP variant was detected on any tumor type by tumor genomic profiling in the absence of germline mutation testing.

7) For individuals less than 18 years of age who have one biological parent with MAP and one unaffected parent, sequencing of the *MUTYH* gene **DOES NOT MEET COVERAGE CRITERIA**.

8) For all other situations not described above, multi-gene panel testing **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: For individuals under 18 years of age, "genetic testing is generally not recommended unless results would impact medical management, such as initiation of early colonoscopy surveillance. Clear exceptions include when familial adenomatous polyposis (FAP), juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), or constitutional MMR deficiency (CMMRD) syndrome are suspected or known to be present in a family, in which case testing prior to age 18 is recommended to guide medical management."[10]

Note 2: Per the NCCN, "multigene panel[s] should include all polyposis and CRC [colorectal cancer] genes."[10] At minimum, multigene panels should include the following polyposis and CRC risk genes: *APC, ATM, AXIN2, BLM, BMPR1A, CHEK2, EPCAM, GALNT12, GREM1, MBD4, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, POLD1, POLE, PMS2, PTEN, RNF43, RPS20, SMAD4, STK11,* and *TP53.*

Note 3: For two or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.

Note 4: A clinical diagnosis of serrated polyposis syndrome (previously known as hyperplastic polyposis) is considered when an individual meets at least one of the following:

- The individual has five* or more serrated lesions/polyps proximal to the rectum, with all polyps being greater than or equal to 5 mm in size and with two or more of those polyps being greater than or equal to 10 mm in size.
- The individual has 21* or more lesions/polyps of any size distributed throughout the large bowel, with five or more being proximal to the rectum.

*Any histologic subtype of serrated lesion/polyp (i.e., hyperplastic polyp, sessile serrated lesion with or without dysplasia, traditional serrated adenoma, unclassified serrated adenoma) is included in the final polyp count. The polyp count is cumulative over multiple colonoscopies.

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IV. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
ACMG	American College of Medical Genetics and Genomics
AFAP	Attenuated familial adenomatous polyposis
AGA	American Gastrointestinal Association
APC	*Adenomatous polyposis coli gene*
ASCRS	American Society of Colon and Rectal Surgeons
ASGE	American Society for Gastrointestinal Endoscopy
AXIN2	*Axis inhibition protein 2 gene*
BMPR1A	*Bone morphogenetic protein receptor, type 1A gene*
CHRPE	Congenital hypertrophy of retinal pigment epithelium
CLIA	Clinical Laboratory Improvement Amendments
CMMRD	Constitutional MMR deficiency
CMS	Centers for Medicare and Medicaid Services
CRC	Colorectal cancer
EHTG	European Hereditary Tumour Group
EPCAM	*Epithelial cell adhesion molecule gene*
EPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
ESCP	European Society of Coloproctology
ESMO	European Society for Medical Oncology
EXO1	*Exonuclease 1 gene*
FAP	Familial adenomatous polyposis
GAPPS	Gastric Adenocarcinoma and Proximal Polyposis of the Stomach
GI	Gastrointestinal
GREM1	*Gremlin 1 gene*
HHT	Hereditary hemorrhagic telangiectasia
JPS	Juvenile polyposis syndrome
KRAS	*Kirsten rat sarcoma virus gene*
~~LDTs~~LDT	Laboratory Developed ~~Tests~~Test
LS	Lynch syndrome
MAP	*MUTYH* Associated Polyposis
MLH1	*MutL protein homolog 1 gene*
MLPA	Multiplex ligation-dependent probe amplification
MMR	Mismatch repair
MSH2	*MutS homolog 2 gene*
MSH3	*MutS homolog 3 gene*
MSH6	*MutS homolog 6 gene*
MUTYH	*mutY DNA glycosylase gene*
OGG1	*8-oxoguanine glycosylase gene*
NCCN	National Comprehensive Cancer Network

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NGS	Next-generation sequencing
NIPT	Noninvasive prenatal testing
NSGC	National Society of Genetic Counselors
NTHL1	*Endonuclease III-like protein 1 gene*
PJS	Peutz-Jeghers syndrome
PMS2	*PMS1 homolog 2, mismatch repair system component gene*
POLD1	*Polymerase delta 1 gene*
POLE	*DNA polymerase epsilon, catalytic subunit gene*
POLQ	*DNA polymerase theta gene*
PTEN	*Phosphatase and tensin homolog gene*
SMAD4	*SMAD family member 4/*Mothers against decapentaplegic homolog 4 *gene*
SPS	Serrated polyposis syndrome
STK11	*Serine/threonine kinase 11 gene*
TGFβ	*Transforming growth factor beta gene*
WES	Whole exome sequencing

V. 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 FAP and *MAP*.[11] Both FAP and MAP account for less than one percent of all colorectal cancer cases.[12,13]

Familial Adenomatous Polyposis results from mutations in the 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.[14] The prevalence of FAP is about 1:13,000.[5] More than 300 different mutations have been reported, and the clinical presentation is dependent on the location of the mutation in the *APC* gene.[4,5] 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.[12] 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.[5] Patients with FAP are also at risk for extracolonic malignancies, such as desmoid tumors, duodenal adenomas, or even brain tumors.[12]

In contrast, mutations in either end of the gene predispose to attenuated FAP (AFAP).[4] 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 on average about 14 years later when compared with classic FAP (44 years of age versus 58 years of age, respectively). Overall, AFAP is a milder, but very similar form, of FAP.[12]

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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.[15] 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. *MAP* 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 *MAP*, but hyperplastic and sessile serrated polyps have been reported in some patients.[13] The genes that are mutated strongly influence the polyposis phenotype with the *KRAS* gene mutation resulting in different phenotypes compared to *MUTYH.*[16] 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.[17,18]

Although both FAP and *MAP* 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 *MAP* is not inherited in this manner. Diagnosis of *MAP* requires identification of biallelic pathogenic germline variants of *MUTYH*.[13]

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 five percent of patients with 10-19 adenomas (50/970). *MUTYH* mutations were found in two percent (2/119), seven percent (94/1338), seven percent (233/3253), and four percent (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. There were 2098 patients out of 8676 (24%) who had a pathogenic *APC* or *MUTYH* mutation, and 6578 (76%) had a non-pathogenic mutation or no mutation in either gene.[19]

Ciavarella, et al. (2018) investigated genetic causes of unexplained adenomatous polyposis in eight 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.[20]

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.[21-24]

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

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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."[25]

Peutz-Jeghers Syndrome (PJS)

Peutz-Jeghers syndrome is another uncommon polyposis syndrome that occurs one in 8,300 to one in 20,000 births.[26] 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 extraintestinal cancers. Pathogenic mutations in the *STK11* gene is most strongly associated with PJS; although not every genetic mutation associated with PJS has been identified.[8]

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.[9]

Jia, et al. (2018) analyzed clinical features of 46 patients with 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". Eleven patients underwent gene sequencing with a panel of 20 genes, and five were found to have gene mutations. Three of these patients were found to have mutations in the *STK11* gene.[27]

In a study by Wu, et al. (2020), direct sequencing using the QIAamp DNA Blood Mini Kit and 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 (seven were missense variants, and 13 variants were truncating). All mutations fell within the coding region spanning exon one and exon eight, and no mutation in exon nine was identified in any of these PJS individuals."[28] 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 noninvasive prenatal testing (NIPT). The parents chose to give birth to this fetus, and melanin spots appeared on the lips at approximately one 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

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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."[28]

Juvenile Polyposis Syndrome (JPS)

Juvenile Polyposis Syndrome is another condition thought to confer additional risk for colorectal and gastric cancer. JPS is caused by variants in the *BMPR1A* 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 TGFβ signal transduction system. In patients with *SMAD4* gene variant, severe polyposis in the stomach or duodenum is highly likely.[29] Similar 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 *BMPR1A* and *SMAD4* genes.[8]

Gonzalez, et al. (2017) evaluated the clinicopathological features of 22 patients with "abundant gastric juvenile-type or hyperplastic-like polyps". There were 14 patients that were diagnosed with JPS an average of 40 years. Out of the 22 cases, 18 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, five of six patients tested harbored a *SMAD4* mutation.[30]

VI. Guidelines and Recommendations

National Comprehensive Cancer Network

The NCCN released updated guidelines in ~~2024~~2025 for hereditary polyposis syndromes, encompassing FAP, MAP, PJS, JPS, Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS), and other related conditions. These updates detail advancements in multigene panel testing (MGPT), criteria for genetic testing, recommended genes, and surveillance strategies for individuals and their families. ~~The NCCN recommends determining personal and familial history with a stepwise approach:~~

1. ~~"First, if an individual has a personal or family history of a known germline pathogenic variant in a colorectal polyposis or cancer gene, further evaluation and management appropriate for established hereditary CRC syndromes is warranted"~~
2. ~~"Second, if there is no known personal or family history of a known pathogenic variant in a colorectal polyposis or cancer gene, the patient's personal history of any of the following should be determined:~~
   - ~~≥10 adenomatous polyps, or~~
   - ~~≥2 hamartomatous polyps, or~~
   - ~~≥5 serrated polyps proximal to the rectum"~~
3. ~~"Third, if the patient has been diagnosed with CRC but personal history is not suspicious for a polyposis syndrome, then the patient should be considered for the evaluation of LS and other cancer risk genes"~~
   - ~~"The NCCN panel has endorsed the following strategies for identifying individuals with LS, and continues to endorse these strategies:~~
     1. ~~Germline multigene panel testing for patients diagnosed with CRC at age <50 years~~
     2. ~~Germline multigene panel testing for individuals at increased risk of a hereditary CRC syndrome based on personal or family history~~

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3. ~~Germline multigene panel testing based on increased model-based risk"~~
4. ~~"Next, personal or family history of other LS-associated cancers beyond CRC should be elicited. LS-associated cancers beyond CRC include: endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome."[10]~~

~~Additionally, the~~The NCCN recommends *APC* or *MUTYH* gene testing for individuals with a known deleterious familial mutation, and individuals with multifocal or bilateral CHRPE. The NCCN recommends that testing be considered in individuals with a personal or family history of CHRPE, osteomas, supernumerary teeth, desmoid tumor, hepatoblastoma, brain cancer (typically medulloblastoma), or cribriform variant of papillary thyroid cancer.[10] If an *APC* variant is found, high-quality colonoscopy every 12 months, beginning at 10 to 15 years of age, is recommended. Colonoscopy is preferred over flexible sigmoidoscopy due to the possibility of missing right-sided polyps when limiting ~~to~~ sigmoidoscopy. However, based on patient and family preference or clinical judgment, sigmoidoscopy may also be considered.[10]

If any of these features are identified, the NCCN recommends genetic counseling before and after testing. "Cancer risk assessment and genetic counseling are highly recommended when genetic testing is offered, including consideration of the most appropriate tests to order (i.e., pre-test counseling), and after results are disclosed (i.e., post-test counseling)."[10]

The NCCN recommends MGPT as a first step to provide a comprehensive evaluation. Testing should include "at a minimum, a germline multigene panel should include the following genes associated with CRC risk: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11*, and *TP53*." MGPT should also be considered for cases involving uncertain histology, inconclusive first-line testing, or limited family history. "Germline MGPT with the following genes that have also been associated with increased risk for polyposis and/or CRC may also be considered: monoallelic PVs in *AXIN2, GREM1, POLE*, and *POLD1*, and biallelic PVs in *MSH3, MLH3, MBD4*, and *NTHL1.*"[10]

The NCCN notes that MGPT is not recommended when the patient's family history is strongly suggestive of a known hereditary syndrome and the individual is from a family with a known pathogenic or likely pathogenic variant and there is no other reason for multigene testing. For these scenarios, they recommend that syndrome-specific panels be considered.[10]

The NCCN also notes the following: "When colonic polyposis is present only in the proband and/or in siblings, consider recessive inheritance or *de novo APC* gene mutations. For example MAP follows a recessive pattern of inheritance, so *MUTYH* testing should be considered if a recessive pattern is apparent in the pedigree…*MUTYH* testing is not indicated based solely on a personal history of a desmoid tumor, hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer."[10]

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/likely pathogenic mutations. "Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is not tested, then comprehensive testing of *MUTYH* should be considered in the children. If the unaffected parent is found to have one *MUTYH* pathogenic variant, then testing the children for the familial *MUTYH* [pathogenic/likely pathogenic] variants is clinically indicated. Testing of 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 first-degree relative affected with CRC, or to inform reproductive risks since their future children could be at risk for MAP."[10]

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The NCCN notes that a classical diagnosis of FAP is suspected when there are "at least 100 cumulative adenomas in the large bowel" present at a young age; however, genetic testing with multigene 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.[10]

The NCCN recommends genetic testing for JPS patients, noting that 50% of cases occur due to pathogenic *SMAD4* or *BMPR1A* mutations. In families with a known BMPR1A pathogenic variant, "genetic testing should be performed by age 12-15 when surveillance would begin (or sooner if symptoms warrant evaluation)." If there is a known familial mutation of *SMAD4*, genetic testing should be performed within the first six months of life. The NCCN also remarks that the majority of PJS cases occur due to pathogenic variants in the *STK11/LKB1* gene.[10]

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 no later than 25-30 years old and performing one every one to two years if negative. If polyps are found, endoscopic evaluation of the rectum every six to twelve months is recommended, depending on polyp burden. 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.

Some general considerations and best practices for genetic testing from the NCCN included the following:

"Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or saliva samples due to unreliable test results from contamination by donor DNA in such cases, DNA of the individual being tested should be extracted from a fibroblast culture from a skin punch biopsy. If this is not possible, buccal cells may be considered as an alternative source of DNA."

"In children < 18y, genetic testing is generally not recommended unless results would impact medical management, such as initiation of early colonoscopy surveillance. Clear exceptions include when FAP, JPS, PJS, or constitutional MMR deficiency (CMMRD) syndrome are suspected or known to be present in a family, in which case testing prior to age 18 is recommended to guide medical management."[10]

American College of Gastroenterology

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."[22] 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.[22]

The 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

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genotyped, all at-risk relatives can be screened properly.[22]

The 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.[22]

American College of Medical Genetics and Genomics

The ACMG has established comprehensive guidelines in 2020 for genetic testing related to inherited CRC and polyposis. Their update in 2021 emphasized the critical role of multigene panel testing in clinical practice. This approach is particularly recommended when "more than one gene may explain a patient's clinical presentation, especially in cases of colonic polyposis of uncertain histology or suspected hereditary cancer syndromes". The guidelines highlight that the clinical sensitivity of multigene panels can vary based on the specific genes included and the patient's clinical presentation. Notably, "at least 10% of patients with CRC harbor pathogenic germline variants identifiable through multigene panel testing, with this figure rising to approximately 20% for individuals diagnosed before age 50."[31]

The ACMG recommends testing for high-risk genes associated with hereditary CRC and polyposis, including "APC, MLH1, MSH2, MSH6, PMS2, and EPCAM," which are linked to conditions such as familial adenomatous polyposis (FAP) and Lynch syndrome. ACMG recommends "that testing should begin with sequencing the entire coding region and splice site boundaries of the APC gene." If no variant is detected, Additional, "sequencing and deletion analysis for MUTYH, POLD1, and POLE are recommended,"[31] as these genes have also been implicated in hereditary colonic polyposis.

"Testing for hereditary colorectal polyposis should be considered for individuals with any of the following:

1. Personal history of 20 or more cumulative adenomas.
2. Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE).
3. Consider testing if a personal history of:
   (a) Between 10 and 19 cumulative adenomas,
   (b) A desmoid tumor,
   (c) Hepatoblastoma,
   (d) Cribriform-morular variant of papillary thyroid cancer,
   (e) Unilateral CHRPE,
   (f) Meets criteria for serrated polyposis syndrome with at least some adenomas."[31]

Universal screening for Lynch syndrome (LS) is recommended in individuals with CRC or endometrial cancer. This is done via microsatellite instability (MSI) testing and/or immunohistochemistry (IHC) for mismatch repair proteins (MMR protein complex: MLH1, MSH2, MSH6, and PMS2) in individuals with CRC or endometrial cancer is recommended."[31] The following testing criteria is specified for testing for LS:

1. "Presence of synchronous or metachronous colorectal cancer or other LS-related tumor regardless of age.

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2. Colorectal cancer in an individual under 60 years of age exhibiting tumor-infiltrating lymphocytes.
3. Colorectal cancer at any age, plus colorectal cancer or LS-related tumor diagnosed before the age of 50 in at least one first-degree relative.
4. Colorectal cancer at any age, plus colorectal cancer or LS-related tumor diagnosed at any age in two or more first-degree or second-degree relatives."[31]

ACMG and the National Society of Genetic Counselors

The 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 five".

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

- "three to five 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:

- "≥ two cumulative histologically proven PJ polyps in the same person"
- "≥ one PJ polyp and mucocutaneous hyperpigmentation in the same person"
- "Any number of PJ polyps and a positive family history of PJS."[23]

European Society for Medical Oncology (ESMO)

The 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."[32]

The ESMO recommends germline testing of *APC* and *MUTYH* for patients with ten 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 considered. If a mutation is detected, testing may also be offered to at-risk family members.[33]

American Society of Colon and Rectal Surgeons (ASCRS)

The ASCRS has established guidelines for the management of polyposis syndromes, emphasizing the

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importance of genetic testing for individuals with a history of colorectal cancer diagnosed before age 50 or those with more than 10 to 20 adenomas. Genetic testing is recommended for patients with 20 or more adenomas, as they have an increased risk of carrying a pathogenic variant. Additionally, individuals with a family history of polyposis should be evaluated, even if no known genetic variant is identified, as de novo mutations can occur. Genetic counseling is advised for patients and at-risk family members, with testing for known familial variants recommended for relatives of affected individuals. The guidelines also highlight the necessity of multigene panel testing to capture a broader range of potential pathogenic variants beyond just APC and MUTYH, as some patients may have polyposis of unknown cause.[34]

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Polyposis Working Group

This Working Group released guidelines on both JPS and 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."[35]

Regarding PJS, the ESPGHAN recommends offering predictive genetic testing for an asymptomatic at-risk child as early as three 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."[36]

American Society for Gastrointestinal Endoscopy (ASGE)

The ASGE released recommendations for the role of genetic testing in the management of patients with FAP syndromes.[37] 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 counseling and testing is recommended "in patients with clinical polyposis defined as 10 or more adenomas found on a single endoscopy and 20 or more adenomas during their lifetime."[37] In addition, genetic counseling is recommended for all patients with or suspected to have FAP syndromes and first-degree relatives.[37]

The *APC* gene testing is recommended "in all first-degree relatives of confirmed polyposis syndrome patients. Suspected FAP individuals should be tested at ages 10 to 12 years, whereas suspected AFAP and MAP should be tested at ages 18 to 20 years."[37] Younger children, aged six months to five years, can

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undergo confirmatory *APC* gene testing if parents agree to screen for hepatoblastoma with alpha-fetoprotein test and liver function test every six months. Otherwise, testing is deferred until 10-12 years old. Children without *APC* gene abnormalities should follow average-risk screening guidelines.[37]

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 two 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 Gastroenterological Association (AGA)

The 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.[38]

European Hereditary Tumour Group and European Society of Coloproctology (EHTG-ESCP)

The EHTG and ESCP jointly released 2024 guidelines for hereditary adenomatous polyposis syndromes, including FAP, MAP, and other rare syndromes like GAPPS. For FAP, genetic testing is recommended as early as 12 years old for asymptomatic patients with a family history or identified APC mutations. Testing for somatic APC mosaicism is advised in cases of unexplained polyposis with more than 20 adenomas.[39]

In cases of MAP, testing for biallelic pathogenic variants in the MUTYH gene is recommended for individuals with multiple adenomas or a family history of colorectal cancer when APC mutations are absent. As MAP is autosomal recessive, testing asymptomatic first-degree relatives is also suggested to assess carrier status.[39]

The MGPT is recommended for patients with clinical presentations such as GI polyposis or overlapping hereditary syndromes and the test "should include APC and MUTYH … as well as other genes relevant for adenomatous polyposis (MMR genes MLH1, MSH2, MSH6, PMS2, MSH3 and MLH3), POLE (exonuclease domain), POLD1 (exonuclease domain), NTHL1, MBD4 and AXIN2. In addition, it is recommended to include genes causing other polyposis syndromes such as STK11, BMPR1A, SMAD4, PTEN and RNF43". The EHTG-ESCP guidelines recommend genetic counseling before and after testing and advocate for family testing in confirmed cases to identify at-risk relatives.[39]

Additionally, rare syndromes, such as GAPPS or those associated with variants in genes like POLE and POLD1, warrant genetic analysis as defined by the following clinical criteria for genetic testing:

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"Essential clinical criteria

1. Phenotypic features
    a. Proximal (body and fundus) gastric polyposis with antral sparing
    b. No evidence of colorectal or duodenal polyposis
    c. >100 polyps carpeting the proximal stomach in the index patient or >30 polyps in a first-degree relative of another patient
    d. Predominantly fundic gland polyps and/or fundic gland–like polyps
2. Proband or family member with either dysplastic fundic gland polyps or gastric adenocarcinoma
3. Mutation in the chr5:112043220_112043224 region of promoter 1B of the APC gene

Supportive clinical criteria

1. Spectrum of other histological lesions:
    a. Hyperproliferative aberrant pits
    b. Hyperplastic polyps
    c. Gastric-type adenomas
2. Family history (autosomal dominant pattern of inheritance)."[39]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

On January 18, 2019, the FDA approved the *MAP* testing by 23andMe, Inc.[40]

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	CPT Description
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants

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81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	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)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81479	Unlisted molecular pathology procedure

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

IX. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

X. Evidence-based Scientific References

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XI. Revision History

Revision Date	Summary of Changes
03/18/2026	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: For clarity and consistency, “pathogenic” was changed to “pathogenic/likely pathogenic (P/LP)” throughout criteria and “mutation” was changed to variant throughout criteria. NCCN updates necessitated updates to polyposis testing criteria. CC3: Removed CC3.a. and moved CC3.a.i. into former CC3.b., now CC3.a., number remains CC3.a.i. Removed CC3.b.iii. Primary brain tumor (e.g., medulloblastoma)., CC3.b.vi. Osteomas, and CC3.b.vii. Supernumerary teeth, as these conditions are no longer included in the genetic testing workflow provided by the NCCN. Added new CC3.b. and CC3.c.: “b) For individuals who meet criteria for serrated polyposis syndrome (see Note 4) with at least some of the qualifying polyps being adenomas. c) For individuals who were diagnosed with any cancer before 30 years of age and for whom an APC P/LP variant was found on tumor-only genomic testing.” New CC5.d.: “d) For individuals for whom a BMPR1A or SMAD4 P/LP variant was detected on any tumor type by tumor genomic profiling in the absence of germline mutation testing.” New CC6.d.: “d) For individuals for whom an STK11 P/LP variant was detected on any tumor type by tumor genomic profiling in the absence of germline mutation testing.” New Note 4 defining serrated polyposis syndrome.

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