Sentara Health Plans

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
Policy Revision Date: 12/01/2024 Initial Policy Effective Date: 12/01/2024	

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 5,000-10,000 individuals in the United States (Kinzler & Vogelstein, 1996; NORD, 2014). 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 (Brosens et al., 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 (Society, 2023).

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 (Nielsen, 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 (Chung, 2023; Chung & Delgado, 2024).

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 polyposis gene variant, the following testing **MEETS COVERAGE CRITERIA:**
   a) Testing restricted to the known pathogenic familial variant.
   b) Comprehensive genetic testing, including muti-gene panel testing (see Note 2), when the specific familial mutation is unknown.

3) For individuals (see Note 1) who have no known familial pathogenic 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 10 or more cumulative adenomas.
   b) For individuals with a personal history of 2 or more hamartomatous polyps.
   c) For individuals with multifocal/bilateral or unilateral congenital hypertrophy of retinal pigment epithelium (CHRPE).
   d) For individuals with a personal history of **any** of the following:
      i) Primary brain tumor (e.g., medulloblastoma).
      ii) Desmoid tumor.
      iii) Hepatoblastoma.
      iv) Osteomas.
      v) Supernumerary teeth.
   e) For individuals who meet the criteria for serrated polyposis syndrome (SPS):
      i) Individual has 5 or more serrated lesions/polyps proximal to the rectum, all being greater than or equal to 5 mm in size, with 2 or more being greater than or equal to 10 mm in size.

ii) Individual has greater than 20 serrated lesions/polyps of any size, distributed throughout the large bowel, with 5 or more being proximal to the rectum.

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 known pathogenic familial *SMAD4* or *BMPR1A* mutations (testing restricted to known pathogenic familial mutation).

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

   c) For individuals with any number of juvenile polyps in other regions of the GI tract.

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

   a) For individuals with a known family history of Peutz-Jeghers syndrome or known pathogenic familial *STK11* mutation (testing restricted to known pathogenic familial mutation).

   b) For individuals with mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes genitalia, or fingers.

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

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), JPS, PHS, 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" (NCCN, 2023).

Note 2: Per the NCCN, "multigene panel[s] should include all polyposis and CRC [colorectal cancer] genes" (NCCN, 2023). 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 2 or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.

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
EPCAM	*Epithelial cell adhesion molecule gene*
EPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
ESMO	European Society for Medical Oncology
EXO1	*Exonuclease 1 gene*
FAP	Familial adenomatous polyposis
GI	Gastrointestinal
GREM1	*Gremlin 1 gene*
HHT	Hereditary hemorrhagic telangiectasia
JPS	Juvenile polyposis syndrome
KRAS	*Kirsten rat sarcoma virus gene*
LDTs	Laboratory Developed Tests
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
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 familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis (MAP) (Jasperson et al., 2010). Both FAP and MAP account for less than one percent of all colorectal cancer cases (Chung & Rodgers, 2024; Grover & Stoffel, 2022).

Familial Adenomatous Polyposis 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 & Lucas, 2023). 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 & Rodgers, 2024). When fully developed, patients can have up to thousands of colorectal adenomas and nearly 100% risk of CRC. About 50% of patients developed adenomas by age 15 and 95% by age 35. If left untreated, FAP patients will

develop CRC at an average age of 39 (Brosens et al., 2015). Patients with FAP are also at risk for extracolonic malignancies, such as desmoid tumors, duodenal adenomas, or even brain tumors (Chung & Rodgers, 2024).

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 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 (Chung & Rodgers, 2024).

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, 2022). 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; Nielsen et al., 2021).

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, 2022).

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 (Grover et al., 2012).

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 (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 et al., 2015; Hegde et al., 2014; Provenzale et al., 2016; Syngal et al., 2015).

In a study by M. 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)

Peutz-Jeghers Syndrome is another uncommon polyposis syndrome that occurs one in 8,300 to one in 20,000 births (Giardiello & Trimbath, 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 (Chung & Delgado, 2024).

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 (Chung, 2023).

Jia et al. (2018) 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". 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 (Jia et al., 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 (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" (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 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 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)

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 (NHS, 2020). 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 (Chung & Delgado, 2024).

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 (Gonzalez et al., 2017).

VI. Guidelines and Recommendations

National Comprehensive Cancer Network

The NCCN recommends *APC* or *MUTYH* gene testing for individuals with a personal history of ≥20 adenomas, individuals with a known deleterious familial mutation, and individuals with multifocal or bilateral congenital hypertrophy of retinal pigment epithelium (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 (Gupta et al., 2017; NCCN, 2023). 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. (NCCN, 2023).

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 or familial history of the following clinical signs:

- ten or more adenomatous polyps
- two or more hamartomatous polyps or
- five or more serrated polyps proximal to the rectum

If any of these features are identified, the NCCN recommends a detailed risk assessment/genetic evaluation for possible 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, and AXIN2, and biallelic pathogenic variants in NTHL1 and MSH3."

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…" (NCCN, 2023).

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" (NCCN, 2023).

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 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, 2023).

NCCN lists clinical scenarios for which multigene 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 tumor and family-based criteria associated with Lynch Syndrome is recommended. Panel testing may be an option if the personal and family histories are "strongly suggestive" of an inherited condition. The panel states that "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*." The NCCN also recommends genetic counseling before and after genetic testing is done (NCCN, 2023).

The NCCN recommends genetic testing for juvenile polyposis syndrome 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 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, 2023).

The 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, 2023; 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 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" (NCCN, 2023).

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" (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).

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 genotyped, all at-risk relatives can be screened properly (Syngal et al., 2015).

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 (Syngal et al., 2015).

American College of Medical Genetics and Genomics

The 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).

The 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

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" (Hampel et al., 2015).

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" (Stjepanovic et al., 2019).

The 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 considered. If a mutation is detected, testing may also be offered to at-risk family members (Balmaña et al., 2013).

American Society of Colon and Rectal Surgeons (ASCRS)

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

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).

Regarding PJS, the 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)

The 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).

The *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 six months to five years, can 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 (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 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 (Boardman et al., 2020).

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 *MUTYH*-Associated Polyposis (MAP) testing by 23andMe, Inc (FDA, 2024).

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
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

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. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
12/01/2024	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Added reference to new Note 3 to CC3, for clarity added “syndrome” behind “polyposis”. Addition of new CC3.b.. Combined CC3.c., d., and e. into new CC3.d, added “brain cancer”, “osteomas”, and “supernumerary teeth”. CC now reads: “3) For individuals (see Note 1) who have no known familial pathogenic 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: b) For individuals with a personal history of 2 or more hamartomatous polyps. d) For individuals with a personal history of any of the following: i) Primary brain tumor (e.g., medulloblastoma). ii) Desmoid tumor. iii) Hepatoblastoma. iv) Osteomas. v) Supernumerary teeth.”

	Addition of polyposis and CRC risk genes to Note 2, note now reads “Note 2: Per the NCCN, “multigene panel[s] should include all polyposis and CRC [colorectal cancer] genes” (NCCN, 2023). 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.” Addition of new Note 3: “Note 3: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.” Removed CPT code 96040, S0265, as genetic counseling is not managed by Avalon
12/01/2024	Initial Policy Implementation