Policy Statement

**APC Testing**
I. Genetic testing of the **APC** gene may be considered **medically necessary** for an individual with **any** of the following:
   A. At-risk relatives (first or second degree) with familial adenomatous polyposis (FAP) and/or a **known APC variant**
   B. Personal history of 20 or more adenomas
   C. Personal history of between 10 to 20 polyps and **one or more** of the following:
      1. First or second degree relative with more than 20 polyps
      2. Other high-risk features as defined by a personal history of desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal or bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE)
   D. When included as part of an approved small genetic **panel**

II. Genetic testing for **APC** gene variants is considered **investigational** for colorectal cancer (CRC) individuals with classical FAP for confirmation of the FAP diagnosis.

III. Testing for germline **APC** gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

**MUTYH Testing**
IV. Genetic testing of the **MUTYH** gene may be considered **medically necessary** for an individual with **any** of the following:
   A. **At-risk** relatives (first or second degree) with a known MUTYH gene variant (single site analysis only)
   B. A negative result for **APC** gene variants (when the criteria for approval of APC testing was met)
   C. When included as part of an approved small genetic **panel**

V. Testing for germline **MUTYH** gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

**MisMatch Repair (MMR) Gene and EPCAM Testing**
VI. Genetic testing for Lynch Syndrome (LS), also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), **MMR** genes (**MLH1, MSH2, MSH6, PMS2**); both initial sequencing and for deletions and duplications) and the EPCAM gene may be considered **medically necessary** for an individual with **any** of the following:
   A. **Family history** of a known LS mutation (Variant single site analysis only)
   B. Personal or family history of colorectal or endometrial cancer diagnosed before 50 years
   C. An individual with CRC or endometrial cancer with tumor testing suggesting germline MMR deficiency (by microsatellite instability-MSI, or loss of mismatch repair protein expression by immunohistochemical-IHC- analysis) or meeting clinical criteria for Lynch syndrome
   D. Personal or **family history** of at least 1 person with colorectal or endometrial cancer and another synchronous or metachronous **Lynch syndrome-related tumor** in the same person
E. Personal (or family history of at least 2 people) with LS-related tumors and at least 1 diagnosed before 50 years of age
F. Personal or family history of at least 3 people with LS-related tumors, regardless of age
G. A 5% or more risk of having an MMR gene mutation based predictive models (e.g. PREMM5, MMRpro, MMRpredict) as documented in the medical record (See policy guidelines for calculators)
H. No diagnosis of colorectal cancer (CRC) but with a family history meeting the Amsterdam criteria, when no affected family members have been tested for MMR variants (See policy guidelines; Revised Bethesda criteria are included in the above criteria)
I. When included as part of an approved small genetic panel

VII. Testing for germline MMR gene variants for inherited CRC syndromes is considered investigational in all other situations.

VIII. Testing for germline EPCAM gene variants for inherited CRC syndromes is considered investigational in all other situations.

SMAD4 and BMPR1A Testing
IX. Genetic testing of SMAD4 and BMPR1A genes may be considered medically necessary when any of the following:
   A. An individual with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
      1. At least 3 to 5 juvenile polyps in the colon
      2. Multiple juvenile polyps found throughout in other parts of the gastrointestinal tract
      3. Any number of juvenile polyps in a person with a known family history of juvenile polyps
   B. At-risk relative of an individual suspected of or diagnosed with juvenile polyposis syndrome
   C. When included as part of an approved small genetic panel

X. Testing for germline SMAD4 and BMPR1A gene variants for inherited CRC syndromes is considered investigational in all other situations.

STK11 Testing
XI. Genetic testing for STK11 gene variants may be considered medically necessary in any of the following:
   A. An individual with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
      1. Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the gastrointestinal tract
      2. Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
      3. Family history of Peutz-Jeghers syndrome
   B. At-risk relative of an individual suspected of or diagnosed with Peutz-Jeghers syndrome
   C. When included as part of an approved small genetic panel

XII. Testing for germline STK11 gene variants for inherited CRC syndromes is considered investigational in all other situations.

Panel Testing
XIII. Limited genetic panels (including at a minimum APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, SMAD4, BMPR1A, and STK11 billed as CPT 81435) may be considered medically necessary as an alternative to serial testing of individual genes when criteria are met for any genetic testing of hereditary colorectal cancer, as indicated by one or more of the following:
   A. Personal history of 20 or more adenomas
   B. Personal history of between 10 to 20 polyps and one of the following:
1. First or second degree relative with more than 20 polyps
2. Other high-risk features as defined by a personal history of desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal or bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE)

C. Family history of a known LS mutation

D. Personal or family history of colorectal or endometrial cancer diagnosed before 50 years

E. Personal history of colorectal or endometrial cancer at any age with tumor showing evidence of mismatch repair deficiency, either by microsatellite instability (MSI) or loss of mismatch repair protein expression by Immunohistochemical (IHC) analysis

F. Personal or family history of at least 1 person with colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-related tumor in the same person

G. Personal (or family history of at least 2 people) with LS-related tumors and at least 1 diagnosed before 50 years of age

H. Personal or family history of at least 3 people with LS-related tumors, regardless of age

I. A 5% or more risk of having an MMR gene mutation based on predictive models (e.g., PREMM5, MMRpro, MMR predict) as documented in the medical record (See policy guidelines for calculators)

J. No diagnosis of colorectal cancer (CRC) but with a family history meeting the Amsterdam criteria, when no affected family members have been tested for MMR variants (See policy guidelines; Revised Bethesda criteria are included in the above criteria)

K. An individual with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
   1. At least 3 to 5 juvenile polyps in the colon
   2. Multiple juvenile polyps in other parts of the gastrointestinal tract
   3. Any number of juvenile polyps with a known family history of juvenile polyps

L. At-risk relative of an individual suspected of or diagnosed with juvenile polyposis syndrome

M. An individual with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
   1. Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine
   2. Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
   3. Family history of Peutz-Jeghers syndrome

N. An individual with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
   1. Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine
   2. Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
   3. Family history of Peutz-Jeghers syndrome

O. To exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a colorectal cancer (CRC) tumor on immunohistochemical (IHC) analysis

XVI. The following are considered investigational:
   A. Large multi-gene panels including multiple genes that are not highly associated with hereditary colorectal cancer
   B. Genetic testing of all other genes for an inherited CRC syndrome

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.
APC/MUTYH mutations (less than 4% of those with Lynch Syndrome [LS] MMR mutations have 10 or more adenomas).

If initial testing is negative, further testing is not automatic, but based on the clinical situation. That is, if initial testing for APC is negative, MMR testing is not automatic; and if initial MMR testing is negative, APC testing is not always needed as a next step.

The Revised Bethesda criteria are included in the reasons for approval.

Adenomas are a type of polyp. There are different kinds of both polyps and adenomas. Adenomas are benign, but some can go on to become cancerous.

Panel Testing
When criteria are met, small panel testing using CPT code 81435 is the broadest testing for Lynch syndrome and inherited colon cancer risk allowed and should be used as an alternative to individual gene testing when criteria are met as outlined in the policy statement above. Examples of such limited tests when billed as 81435 may include the myRisk (may also be billed as CPT 81432) or Colaris® panel from Myriad laboratories, the Colonette panel from Ambry, or a Colorectal Cancer Panel by Invitae). If individual or smaller panel testing meeting criteria is performed initially, any remaining genes (including those in the 81435 panel) that are not included individually in the medically necessary criteria above are considered investigational and are not covered when requested at a later time.

Claims for panel testing should reflect the CPT code closest to the panel being ordered (81435). Claims submitted using individual gene codes rather than the appropriate panel code is considered to be unbundling and improper coding.

Testing related to hereditary breast and ovarian cancer, see Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2).

Panel testing related to cancers other than breast, ovarian, colorectal, and non-small-cell lung cancer, see Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing.

Testing At-Risk Relatives
Due to the high lifetime risk of cancer of most genetic syndromes discussed in this policy, “at-risk relatives” primarily refers to first or second degree relatives. However, some judgment must be permitted, e.g., in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.

Targeted Familial Variant Testing
It is recommended that, when possible, initial genetic testing for familial adenomatous polyposis (FAP) or Lynch syndrome be performed in an affected family member, so that testing in unaffected family members can focus on the variant found in the affected family member (see Benefit Application section). If an affected family member is not available for testing, testing should begin with an unaffected family member most closely related to an affected family member.

In many cases, genetic testing for MUTYH gene variants should first target the specific variants Y165C and G382D, which account for more than 80% of variants in white populations, and subsequently, proceed to sequence only as necessary. However, in other ethnic populations, proceeding directly to sequencing is appropriate. Full gene testing is most commonly requested and can be approved without doing the common variants first.
**Known Variant Testing**

Known variant testing should be limited to that (site specific) analysis only, rather than the whole gene.

**High-risk features for MUTYH gene variants:**

The following may also be considered as high-risk features for MUTYH gene variants:

- At least 5 serrated polyps (includes hyperplastic polyps, sessile serrated adenomas or polyps, and traditional serrated adenomas) proximal to the sigmoid colon with 2 or more greater than 10 millimeters (mm)
- 20 or more serrated polyps of any size distributed throughout the colon

**Note:** A family history of no parents or children with FAP is consistent with MUTYH-Associated Polyposis (MAP, which is autosomal recessive).

**Lynch Syndrome-Related Tumors**

Lynch syndrome-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

**Family History**

Family history refers to first- or second-degree relatives.

**Hamartomatous and Serrated Polyps**

Two or more hamartomatous polyps or five or more serrated polyps may need different genetic testing (see NCCN guidelines).

**Evaluation for Lynch Syndrome**

For patients with colorectal cancer (CRC) or endometrial cancer being evaluated for Lynch syndrome, the microsatellite instability (MSI) test or the immunohistochemical (IHC) test with or without **BRAF** gene variant testing, or methylation testing, should be used as an initial evaluation of tumor tissue before mismatch repair (MMR) gene analysis. Both tests are not necessary. Proceeding to MMR gene sequencing would depend on the results of MSI or IHC testing. In particular, IHC testing may help direct which MMR gene likely contains a variant, if any, and may also provide additional information if MMR genetic testing is inconclusive. MMR testing may still be needed, and can be approved without MSI or IHC test results. For further information on tumor tissue test results, interpretation, and additional testing options, see the [NCCN (National Comprehensive Cancer Network) clinical care guidelines on genetic/familial high risk assessment: colorectal](http://nationalcomprehensivecancernetwork.org).

MLH1 and MSH2 variants are most common, but testing is usually done in a panel that includes MSH6 and PMS2 and sometimes EPCAM. Standard sequencing methods will not detect large deletions or duplications so testing for large deletions or duplications is appropriate and is usually done at the same time as initial MMR sequence testing.

**Amsterdam II Clinical Criteria**

The Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent for defining families at high risk for Lynch syndrome:

- 3 or more relatives with an associated cancer (CRC, or cancer of the endometrium, small intestine, ureter, or renal pelvis)
- 1 should be a first-degree relative of the other 2
- 2 or more successive generations affected
- 1 or more relatives diagnosed before the age of 50 years
- FAP should be excluded in cases of CRC
- Tumors should be verified by pathologic examination
- Modifications:
EITHER: very small families, which cannot be further expanded, can be considered to have hereditary nonpolyposis colorectal cancer (HNPCC) with only 2 CRCs in first-degree relatives if at least 2 generations have the cancer and at least 1 case of CRC was diagnosed by the age of 55 years

OR: in families with 2 first-degree relatives affected by CRC, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient

Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are available such MMRpro, PREMM5, or MMRpredict. National Comprehensive Cancer Network guidelines recommend (category 2A) testing for Lynch syndrome in individuals with a 5% or higher predicted risk of the syndrome on these risk prediction models.

These quantitative estimates of the likelihood of an MMR variant can be ascertained by the use of the following, available calculators:

- **PREMM5**: http://premm.dfci.harvard.edu/
- **MMRpro**: https://projects.iq.harvard.edu/bayesmendel/mmrpro
- **MMRpredict**: https://webapps.igc.ed.ac.uk/world/research/hnpccpredict/

**Genetic Counseling**
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Coding**
There is a CPT that represents Genomic Unity® Lynch Syndrome Analysis by Variantyx Inc. Per the manufacturer, this test is for individuals with or suspected of having Lynch syndrome. Genomic DNA isolated from blood or saliva is sequenced, examined for deviations or variants in the Lynch Syndrome related genes and evaluated for potential impact on protein function and pathogenicity based on American College of Medical Genetics guidelines. This service may have been previously billed using CPT codes 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81479.

- **0238U**: Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

The following CPT PLA code represents the Ambry Genetics® APC mRNA sequence analysis panel:

- **0157U**: APC (APC regulator of WNT signaling pathway) (e.g., familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use in conjunction with CPT code 81201)

The following CPT PLA code represents the Ambry Genetics® MLH1 mRNA sequence analysis panel:

- **0158U**: MLH1 (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use in conjunction with CPT code 81292)
The following CPT PLA code represents the Ambry Genetics® MSH2 mRNA sequence analysis panel:
- **0159U**: MSH2 (mutS homolog 2) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use in conjunction with CPT code 81295)

The following CPT PLA code represents the Ambry Genetics® MSH6 mRNA sequence analysis panel:
- **0160U**: MSH6 (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use in conjunction with CPT code 81298)

The following CPT PLA code represents the Ambry Genetics® PMS2 mRNA sequence analysis panel:
- **0161U**: PMS2 (PMS1 homolog 2, mismatch repair system component) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use in conjunction with CPT code 81317)

The following CPT PLA code represents the Ambry Genetics® Lynch (MLH1, MSH2, MSH6, PMS2) mRNA sequence analysis panel:
- **0162U**: Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure) (Use in conjunction with CPT codes 81292, 81295, 81298, 81317, 81435)

The following CPT PLA code represents the +RNAinsight™ for ColoNext® mRNA sequence analysis panel:
- **0130U**: Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)

There are specific CPT codes for genetic testing of APC:
- **81201-81203**: APC genetic testing code range

There are specific CPT codes for genetic testing of MLH1, MSH2, MSH6, PMS2, and microsatellite instability:
- **81288**: MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
- **81292-81294**: MLH1 genetic testing code range
- **81295-81297**: MSH2 genetic testing code range
- **81298-81300**: MSH6 genetic testing code range
- **81301**: Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
- **81317-81319**: PMS2 genetic testing code range

The following CPT code includes testing for EPCAM:
- **81403**: Molecular Pathology Procedure Level 4. EPCAM (epithelial cell adhesion molecule) (e.g., Lynch syndrome), duplication/deletion analysis

The following CPT code may be billed for panel testing:
- **81435**: Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPRIA, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
Genetic testing for colon cancer is not widely available and is most commonly performed by commercial reference labs or research labs dedicated to genetic testing in general.

Associated genetic counseling performed by a trained genetic counselor would be coded using the following CPT code:

- **96040**: Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

Genetic counseling performed by a provider is coded using the appropriate CPT evaluation and management codes.

### Description

Genetic testing is available for both those with and those at risk for various types of hereditary cancer. This review evaluates genetic testing for hereditary colorectal cancer (CRC) and polyposis syndromes, including familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), *MUTYH*-associated polyposis (MAP), Lynch syndrome-related endometrial cancer, juvenile polyposis syndrome (JPS), and Peutz-Jeghers syndrome (PJS).

### Related Policies

- **N/A**

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

### Regulatory Status

**FDA:**
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic tests reviewed in this evidence review are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**State:**
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker...
Rationale

Background
Hereditary Colorectal Cancers
Currently, 2 types of hereditary colorectal cancers (CRCs) are well-defined: familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis CRC). Lynch syndrome has been implicated in some endometrial cancers as well.

Familial Adenomatous Polyposis and Associated Variants
Familial adenomatous polyposis typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will develop CRC. The mean age of colon cancer diagnosis in untreated individuals is 39 years. The condition accounts for about 1% of CRC and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina referred to as congenital hypertrophy of the retinal pigment epithelium. Familial adenomatous polyposis associated with these collective extraintestinal manifestations is sometimes referred to as Gardner syndrome. This condition may also be related to central nervous system tumors, referred to as Turcot syndrome.

Germline variants in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Variants in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. A specific APC gene variant (I1307K) has been found in Ashkenazi Jewish descendants, which may explain a portion of the familial CRC occurring in this population.

A subset of FAP patients may have an attenuated form of FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP. In the attenuated form of FAP, CRC occurs at an average age of 50 to 55 years, but the lifetime risk of CRC remains high (>70% by age 80 years). The risk of extraintestinal cancer is also lower but cumulative lifetime risk remains high (>38%) compared with the general population. Only 30% or fewer of attenuated FAP patients have APC variants; some of these patients have variants in the MUTYH (formerly MYH) gene, and this form of the condition is called MUTYH-associated polyposis (MAP). This form of polyposis occurs with a frequency similar to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH variants are associated with a cumulative CRC risk of about 80% by age 70, whereas the monoallelic MUTYH variant-associated risk of CRC appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (i.e., between 10 and 99) adenomas are present, and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include APC, MUTYH if APC is negative for variants, and screening for variants associated with Lynch syndrome.

It is important to distinguish between classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary by syndrome.

Testing
Genetic testing for APC variants may be considered in the following situations:

- Patients at high-risk, such as those with a family member who tested positive for FAP and have a known APC variant.
• Patients undergoing differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome. These patients do not meet the clinical diagnostic criteria for classical FAP and have few adenomatous colonic polyps.
• To confirm FAP in patients with colon cancer with a clinical picture or family history consistent with classical FAP.

Lynch Syndrome
Lynch syndrome is an inherited disorder that results in a higher predisposition to CRC and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3% to 5% of all CRC. People with Lynch syndrome have a 70% to 80% lifetime risk of developing any type of cancer.\(^5,6\) However, the risk varies by genotype. It occurs as a result of germline variants in the mismatch repair (MMR) genes that include MLH1, MSH2, MSH6, and PMS2. In approximately 80% of cases, the variants are located in the MLH1 and MSH2 genes, while 10% to 12% of variants are located in the MSH6 gene, and 2% to 3% in the PMS2 gene. Additionally, variants in 3 additional genes (MLH3, PMS1, EX01) have been implicated with Lynch Syndrome. Notably, in individuals meeting the various clinical criteria for Lynch syndrome, 50% of individuals have a variant in the MLH1, MSH2, MSH6, and PMS2 genes. The lifetime risk of CRC is nearly 80% in individuals carrying a variant in 1 of these genes.

Testing
Preliminary screening of tumor tissue does not identify MMR gene variants but is used to guide subsequent diagnostic testing via DNA analysis for specific variants. Genetic testing or DNA analysis (gene sequencing, deletion, and duplication testing) for the MMR genes involves assessment for MLH1, MSH2, MSH6, and PMS2 variants. The following are 3 testing strategies.
• Microsatellite instability (MSI) testing (phenotype): Individuals with high MSI either proceed to genetic testing for MLH1, MSH2, MSH6, and PMS2 or to immunohistochemical (IHC) testing.
• IHC testing (phenotype): Individuals with negative staining would proceed to genetic testing for MLH1, MSH2, MSH6, and PMS2.
• Modification strategy: Tumor tissue of patients with negative staining for MLH1 on IHC is tested for the BRAF V600E variant to determine methylation status. If the BRAF variant is not detected, the individual receives MLH1 DNA analysis.

The phenotype tests used to identify individuals who may be at a high risk of Lynch syndrome are explained next. The first screening test measures MSI. As a result of variance in the MMR gene family, the MMR protein is either absent or deficient, resulting in an inability to correct DNA replication errors causing MSI. Approximately 80% to 90% of Lynch syndrome CRC tumors have MSI. The National Cancer Institute has recommended screening for 5 markers to detect MSI (Bethesda markers). Microsatellite instability detection in 2 of these markers is considered a positive result or “high probability of MSI.”\(^6\)

The second phenotype screening test is IHC, which involves the staining of tumor tissue for the presence of 4 MMR proteins (MLH1, MSH2, MSH6, PMS2). The absence of 1 or more of these proteins is considered abnormal.

BRAF testing is an optional screening method that may be used in conjunction with IHC testing for MLH1 to improve efficiency. Methylation analysis of the MLH1 gene can largely substitute for BRAF testing, or be used in combination to improve efficiency slightly.

Both MSI and IHC have a 5% to 10% false-negative rate. Microsatellite instability testing performance depends on the specific MMR variant. Screening with MSI has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6 and a specificity of about 90% for each. The specificity of MSI testing is low because approximately 10% of sporadic CRCs are MSI-positive due to somatic hypermethylation of the MLH1 promoter. Additionally, some tumors positive for MSH6 variants are
associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR variant testing.\textsuperscript{7,8} Immunohistochemical screening has a sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for each.

Screening of tumor tissue from patients enables genetic testing for a definitive diagnosis of Lynch syndrome and leads to counseling, cancer surveillance (e.g., through frequent colonoscopic or endometrial screening examinations), and prophylaxis (e.g., risk-reducing colorectal or gynecologic surgeries) for CRC patients, as well as for their family members.

Genetic testing for an MMR gene variant is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2. The BRAF gene is often mutated in CRC when a particular BRAF variant (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present. To date, no MLH1 gene variants have been reported.\textsuperscript{9} Therefore, patients negative for MLH1 protein expression by IHC, and therefore potentially positive for an MLH1 variant, could first be screened for a BRAF variant. BRAF-positive samples need not be further tested by MLH1 sequencing. MLH1 gene methylation largely correlates with the presence of BRAF V600E and, in combination with BRAF testing, can accurately separate Lynch from sporadic CRC in IHC MLH1-negative cases.\textsuperscript{10}

Novel deletions have been reported to affect the expression of the MSH2 gene in the absence of an MSH2 gene variant, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule, are responsible. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high and/or IHC testing shows a lack of MSH2 expression, but no MSH2 variant is found by sequencing. EPCAM is found just upstream, in a transcriptional sense, of MSH2. Deletions of EPCAM that encompass the last 2 exons of the EPCAM gene, including the polyadenylation signal that normally ends transcription of DNA into messenger RNA, result in transcriptional “read-through” and subsequent hypermethylation of the nearby and downstream MSH2 promoter. This hypermethylation prevents normal MSH2 protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an MSH2 variant prevents MSH2 gene expression.\textsuperscript{11}

Distinct from patients with EPCAM deletions, rare cases of Lynch syndrome have been reported without detectable germline MMR variants, although IHC testing demonstrated a loss of expression of 1 of the MMR proteins. In at least some of these cases, research has identified germline “epivariants,” i.e., methylation of promoter regions that control the expression of the MMR genes.\textsuperscript{11,12,13} Such methylation may be isolated or be in conjunction with a linked genetic alteration near the affected MMR gene. The germline epivariants may arise de novo or may be heritable in Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic CRC wherein the tumor tissue may show MLH1 promoter methylation and IHC nonexpression, but the same is not true of germline cells. Clinical testing for Lynch syndrome-related germline epivariants is not routine but may help in exceptional cases.

Female patients with Lynch syndrome have a predisposition to endometrial cancer. Lynch syndrome is estimated to account for 2% of all endometrial cancers in women and 10% of endometrial cancers in women younger than 50 years of age. Female carriers of the germline variants MLH1, MSH2, MSH6, and PMS2 have an estimated 40% to 62% lifetime risk of developing endometrial cancer, as well as a 4% to 12% lifetime risk of ovarian cancer.

Population Selection
Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR variants, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria\textsuperscript{14} (low sensitivity but high specificity), revised Bethesda guidelines\textsuperscript{15} (better sensitivity but poorer specificity), and risk prediction models (e.g., MMRpro; PREMM5; MMRpredict).\textsuperscript{16} While family history is an important risk factor and should not be discounted in counseling families, it has poor sensitivity and specificity for identifying Lynch syndrome. Based on this and other evidence, the Evaluation of Genomic Applications in Practice and
Prevention Working Group recommended testing all newly diagnosed CRC patients for Lynch syndrome, using a screening strategy based on MSI or IHC (with or without \(BRAF\)) followed by sequencing in screen-positive patients. This recommendation includes genetic testing for the following types of patients:

- Family members of Lynch syndrome patients with a known MMR variant; family members would be tested only for the family variant; those testing positive would benefit from early and increased surveillance to prevent future CRC.
- Patients with a differential diagnosis of Lynch syndrome versus attenuated FAP versus MAP.
- For Lynch syndrome patients, genetic testing of the proband with CRC likely benefits the proband where Lynch syndrome is identified, and appropriate surveillance for associated malignancies can be initiated and maintained, benefiting family members by identifying the family variant.

**Juvenile Polyposis Syndrome**

Juvenile polyposis syndrome (JPS) is an autosomal dominant genetic disorder characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract. It is rare, with an estimated incidence of 1 in 100,000 to 160,000. Generalized JPS refers to polyps in the upper and lower gastrointestinal tract, and juvenile polyposis coli refers to polyps of the colon and rectum. Those with JPS are at a higher risk for CRC and gastric cancer. Approximately 60% of patients with JPS have a germline variant in the \(BMPR1A\) gene or the \(SMAD4\) gene. Approximately 25% of patients have de novo variants. In most cases, polyps appear in the first decade of life and most patients are symptomatic by age 20 years. Rectal bleeding is the most common presenting symptom, occurring in more than half of patients. Other presenting symptoms include prolapsing polyp, melena, pain, iron deficiency anemia, and diarrhea.

As noted, individuals with JPS are at increased risk for CRC and gastric cancer. By 35 years of age, the cumulative risk of CRC is 17% to 22%, which increases to 68% by age 60 years. The estimated lifetime risk of gastric cancer is 20% to 30%, with a mean age at diagnosis of 58 years. Juvenile polyposis syndrome may also be associated with hereditary hemorrhagic telangiectasia. The most common clinical manifestations of hereditary hemorrhagic telangiectasia are telangiectasias of the skin and buccal mucosa, epistaxis, and iron deficiency anemia from bleeding.

**Diagnosis**

A clinical diagnosis of JPS is made on the basis of the presence of any 1 of the following: at least 5 juvenile polyps in the colon or multiple juvenile polyps in other parts of the gastrointestinal tract or any number of juvenile polyps in a person with a known family history of juvenile polyps. It is recommended that individuals who meet clinical criteria for JPS undergo genetic testing for a germline variant in the \(BMPR1A\) and \(SMAD4\) genes for a confirmatory diagnosis of JPS and to counsel at-risk family members. If there is a known \(SMAD4\) variant in the family, genetic testing should be performed within the first 6 months of life due to hereditary hemorrhagic telangiectasia risk.

**Peutz-Jeghers Syndrome**

Peutz-Jeghers syndrome (PJS) is also an autosomal dominant genetic disorder, similar to JPS, and is characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and nongastrointestinal cancers. It is rare, with an estimated incidence of 1 in 8000 to 200,000. In most cases, a germline variant in the \(STK11\) (\(LKB1\)) gene is responsible for PJS, which has a high penetrance of over 90% by the age of 30 years. However, 10% to 20% of individuals with PJS have no family history and are presumed to have PJS due to de novo variants. A variant in \(STK11\) is detected in only 50% to 80% of families with PJS, suggesting that there is a second PJS gene locus.

The reported lifetime risk for any cancer is between 37% and 93% among those diagnosed with PJS with an average age of cancer diagnosis at 42 years. The most common sites for malignancy are the
colon and rectum, followed by breast, stomach, small bowel, and pancreas.\textsuperscript{32} The estimated lifetime risk of gastrointestinal cancer ranges from 38\% to 66\%.\textsuperscript{32} Lifetime cancer risk stratified by organ site is colon and rectum (39\%), stomach (29\%), small bowel (13\%), and pancreas (11\% to 36\%).

**Diagnosis**
A clinical diagnosis of PJS is made if an individual meets 2 or more of the following criteria: presence of 2 or more histologically confirmed PJ polyps of the small intestine or characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, fingers, or family history of PJS.\textsuperscript{26} Individuals who meet clinical criteria for PJS should undergo genetic testing for a germline variant in the STK11 gene for a confirmatory diagnosis of PJS and counseling at-risk family members.

**Literature Review**
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA [Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual]; Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

**Genetic Testing for Familial Adenomatous Polyposis and MUTYH-Associated Polyposis**

**Clinical Context and Test Purpose**
The purpose of genetic testing for familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP) is to

- Identify at-risk relatives of individuals with FAP and/or a known adenomatous polyposis coli (APC) gene variant.
- Make a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome.

The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest is at-risk relatives of individuals with FAP and/or a known APC variant or those who require a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome.

**Interventions**
The relevant intervention is genetic testing for APC or MUTYH. Commercial testing is available from numerous companies.

**Comparators**
The following practice is currently being used to make decisions about managing FAP and MAP: no genetic testing.
Outcomes
The potential beneficial outcomes of primary interest would be the early detection of colorectal cancer (CRC) and appropriate and timely interventional strategies (e.g., endoscopic resection, colectomy) to prolong life.
The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Genetic testing for FAP may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual having or developing FAP.

Study Selection Criteria
For the evaluation of the clinical validity of the genetic test, studies that meet the following eligibility criterion were considered:
- Reported on the analytic sensitivity and specificity and/or diagnostic yield of the test.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
The evidence review for FAP genetic testing was initially informed by a TEC Assessment (1998). Additional information on attenuated FAP and on MAP diagnostic criteria and genetic testing is based on several publications that build on prior, cited research. 

Clinical sensitivity for classic FAP is about 95%; about 90% of pathogenic variants are detected by sequencing, while 8% to 12% of pathogenic variants are detected by deletion and duplication testing. Among Northern European whites, 98% of pathogenic MUTYH variants are detected by full gene sequencing.

A comprehensive review of the APC pathogenic variant and its association with classical FAP and attenuated FAP and MAP is beyond the scope of this evidence review. The likelihood of detecting an APC pathogenic variant is highly dependent on the severity of colonic polyposis and family history. Detection rates are higher in classic polyposis (88%) than in nonclassical FAPs such as attenuated colonic phenotypes (57%) or MAP (33%).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified assessing the clinical utility of genetic testing for FAP and MAP.

Chain of Evidence
Genetic testing of patients requiring a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome may have clinical utility:
• If the test supports the clinical diagnosis of an attenuated disease, the protocol for endoscopic surveillance is affected and, depending on the situation, may avoid more frequent but unnecessary surveillance or necessitates more frequent surveillance.

Genetic testing of at-risk relatives of patients with FAP and/or a known APC variant may have clinical utility:
• If, in the absence of genetic testing, the diagnosis of colorectal polyposis in at-risk relatives of patients with FAP and/or a known APC variant can only be established by colonoscopy and subsequent histologic examination of removed polyps, which are burdensome.
• If results are negative, the test results may provide release from the intensified screening program resulting in psychological relief.

A TEC Assessment (1998) offered the following conclusions:
• Genetic testing for FAP may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.
• At-risk subjects are considered to be those with greater than 10 adenomatous polyps or close relatives of patients with clinically diagnosed FAP or of patients with an identified APC variant.
• The optimal testing strategy is to define the specific genetic variant in an affected family member and then test the unaffected family members to see if they have inherited the same variant.

Testing for the APC variant has no role in the evaluation, diagnosis, or treatment of patients with classical FAP where the diagnosis and treatment are based on the clinical presentation.

Section Summary: Genetic Testing for Familial Adenomatous Polyposis and MUTYH-Associated Polyposis
The analytic and clinical sensitivity and specificity for APC and MUTYH are high. About 90% of pathogenic variants in classical FAP are detected by sequencing while 8% to 12% of pathogenic variants are detected by deletion and duplication testing. Among Northern European whites, 98% of pathogenic MUTYH variants are detected by full gene sequencing. The likelihood of detecting an APC pathogenic variant is highly dependent on the severity of colonic polyposis and family history. Detection rates are higher in classic polyposis (88%) than in nonclassical FAPs such as attenuated colonic phenotypes (57%) or MAP (33%). Direct evidence of clinical utility for genetic testing of attenuated FAP is not available. Genetic testing of at-risk relatives of patients with FAP and/or a known APC variant or those requiring a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from an intensified screening program resulting in psychological relief, and improving health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy.

Lynch Syndrome and Colorectal Cancer Genetic Testing
Clinical Context and Test Purpose
The purpose of genetic testing for Lynch syndrome is to:
• Detect Lynch syndrome in individuals diagnosed with CRC or endometrial cancer,
• Identify at-risk relatives of individuals with a diagnosed Lynch syndrome and/or a known mismatch repair (MMR) variant and/or positive family history meeting Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model,
• Make a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome.

The following PICO was used to select literature to inform this review.
**Populations**
The relevant populations of interest are individuals diagnosed with CRC or endometrial cancer or at-risk relatives of patients with a diagnosed Lynch syndrome and/or a known MMR variant and/or positive family history meeting Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model, or those requiring a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome.

**Interventions**
The relevant intervention is genetic testing for the MLH1, MSH2, MSH6, PMS2, EPCAM, and/or BRAFV600E genes. Commercial testing is available from numerous companies.

**Comparators**
The following practice is currently being used to make decisions about managing Lynch syndrome: no genetic testing.

**Outcomes**
The potential beneficial outcomes of primary interest would be early detection of Lynch syndrome and appropriate and timely interventional strategies (e.g., increased surveillance, endoscopic resection, colectomy) to prolong life.

The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse effects from that treatment or undertreatment.

Genetic testing for Lynch syndrome may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual having or developing Lynch syndrome.

**Study Selection Criteria**
For the evaluation of the clinical validity of the genetic test, studies that met the following eligibility criterion were considered:

- Reported on the analytic sensitivity and specificity and/or diagnostic yield of the test.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Review of Evidence**

**MMR Genes**
Microsatellite instability (MSI) and immunohistochemical (IHC) screening tests for MMR variants have similar sensitivity and specificity. Microsatellite instability screening has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6 and a specificity of about 90% for all. Immunohistochemical screening has sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for each.

The evidence for Lynch syndrome genetic testing in patients with CRC is based on an evidence report conducted for the Agency for Healthcare Research and Quality by Bonis et al (2007), a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009), and an EGAPP recommendation (2009) for genetic testing in CRC. Based on the Agency for Healthcare Research and Quality report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for MMR variants in patients already diagnosed with CRC:
• Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for MMR variant testing and should not be used as a sole determinant or screening test.

• Optional \textit{BRAF} testing can be used to reduce the number of patients, who are negative for \textit{MLH1} expression by IHC, needing \textit{MLH1} gene sequencing, thus improving efficiency without reducing sensitivity for MMR variants.

Vos et al (2020) evaluated the yield to detect Lynch syndrome in a prospective cohort of 3602 newly diagnosed CRC cases below age 70.\textsuperscript{50} The standard testing protocol included IHC or MSI testing, followed by \textit{MLH1} hypermethylation testing. Testing identified \textit{MLH1} hypermethylation in a majority of cases tested (66\% of 264). The percentage of MMR deficient CRC explained by hypermethylation increased with age, while the percentage of patients with hereditary CCR decreased with age. Of the 47 patients who underwent genetic testing, 55\% (26/47) were determined to have Lynch syndrome. The authors estimated that only 78\% of these cases would have been identified by the revised Bethesda guidelines. The percentage by age was 86\% (6/7) in those under 40 years, 57\% (17/29) in patients aged 40 to 64 years, and 30\% (3/10) in patients 65 to 69 years of age and the number needed to test to identify 1 case of Lynch syndrome after prescreening was 1.2 (95\% confidence interval [CI], 1.0 to 2.0) in patients under 40 years, 4.1 (95\% CI, 3.1 to 5.5) in patients 40 to 64 years of age, and 21 (95\% CI, 11 to 43) in CRC patients aged 65 to 69.

Tsuruta et al (2022) performed IHC screening for MMR-related genes (\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2}) to determine the extent to which Lynch syndrome can be diagnosed in patients with endometrial cancer through universal screening.\textsuperscript{51} Samples were obtained from 100 patients, and 19 patients with lost results for any of the proteins were identified. The MSI-high phenotype was identified in 16 of 19 patients and \textit{MLH1} methylation was identified in 11 of 19 patients. The following were also detected: 2 pathological variants (\textit{MSH2} and \textit{MSH6}), 2 cases of unclassified variant (\textit{MSH6}), and 1 case of benign variant (\textit{PMS2}).

\textbf{EPCAM Testing}

Several studies have characterized \textit{EPCAM} deletions, established their correlation with the presence of \textit{EPCAM-MSH2} fusion messenger RNAs (apparently nonfunctional) and with the presence of \textit{MSH2} promoter hypermethylation, and, most importantly, have shown the cosegregation of these \textit{EPCAM} variants with Lynch-like disease in families.\textsuperscript{11,52-56} Because studies differ slightly in how patients were selected, the prevalence of these \textit{EPCAM} variants is difficult to estimate but may be in the range of 20\% to 40\% of patients/families who meet Lynch syndrome criteria, do not have an MMR variant, but have MSI-high tumor tissue. Kempers et al (2011) reported that carriers of an \textit{EPCAM} deletion had a 75\% (95\% CI, 65\% to 85\%) cumulative risk of CRC by age 70 years, which did not differ significantly from that of carriers of an \textit{MSH2} deletion (77\%; 95\% CI, 64\% to 90\%). The mean age at diagnosis was 43 years.\textsuperscript{57} However, the cumulative risk of endometrial cancer was low at 12\% (95\% CI, 0\% to 27\%) by age 70 compared with carriers of an \textit{MSH2} variant (51\%; 95\% CI, 33\% to 69\%; \textit{p}<.001).

\textbf{BRAF V600 or MLH1 Promoter Methylation}

Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients.\textsuperscript{58} \textit{MLH1} and \textit{PMS2} protein stains were absent in 65 patients who were subsequently tested for a \textit{BRAF} variant. Thirty-six (55\%) of the 65 patients had the \textit{BRAF}V600E variant, thus eliminating the need for further genetic testing or counseling for Lynch syndrome. Capper et al (2013) reported on a technique of V600E IHC testing for \textit{BRAF} variants on a series of 91 stratified as high MSI CRC patients.\textsuperscript{59} V600E positive lesions were detected in 21\% of \textit{MLH1}-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore, V600E IHC testing for \textit{BRAF} could be an alternative to \textit{MLH1} promoter methylation analysis. To summarize, \textit{BRAF}V600E variant or \textit{MLH1} promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of \textit{MLH1} protein expression. The presence of \textit{BRAF}V600E or absence of \textit{MLH1} protein expression due
to MLH1 promoter methylation rarely occurs in Lynch syndrome and would eliminate the need for further germline variant analysis for a Lynch syndrome diagnosis.60.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing the clinical utility of genetic testing for Lynch syndrome.

**Chain of Evidence**
Genetic testing of patients with colon or endometrial cancer to detect Lynch syndrome has clinical utility:
- To make decisions about the preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis or segmental colectomy).

Genetic testing of at-risk relatives of patients with Lynch syndrome and/or a known MMR variant and/or positive family history meeting Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model, has clinical utility:
- If the individuals diagnosed with Lynch syndrome are recommended for screening for Lynch syndrome-associated cancers.
- If, in the absence of genetic testing, the diagnosis of Lynch syndrome in at-risk relatives of patients can only be established by colonoscopy and subsequent histologic examination of excised polyps, which is burdensome.
- If negative test results in prompt release from an intensified screening program, thereby reducing an emotional burden.

Genetic testing of patients requiring a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome may have clinical utility:
- If the test supports the clinical diagnosis of Lynch syndrome, the protocol for endoscopic surveillance is affected and, depending on the situation, may avoid more frequent but unnecessary surveillance or necessitates more frequent surveillance.

A chain of evidence can be constructed for the clinical utility of testing all patients with CRC for MMR variants. EGAPP conclusions are summarized next.
- Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients.61-67 About half of the relatives received counseling, and 95% of them chose MMR gene variant testing. Among those positive for MMR gene variants, uptake of colonoscopic surveillance beginning at age 20 to 25 years was high at 53% to 100%.
  - One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance versus those who did not.
  - Surveillance and prevention for other Lynch syndrome cancers.
- The chain of evidence from descriptive studies and expert opinion is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., the index patient).
Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.

Surveillance and prevention for other Lynch syndrome cancers:
- While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In a retrospective study by Schmeler et al (2006), 315 women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.68;
- In a study by Bouzourene et al (2010), surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown.10. Transvaginal ultrasound is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, transvaginal ultrasound in conjunction with endometrial biopsy has been recommended for surveillance.
- Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supporting evidence.

The Cancer Genetic Studies Consortium (1997) recommended that if CRC is diagnosed in patients with an identified variant or a strong family history, a subtotal colectomy with ileorectal anastomosis should be considered as an option for segmental resection.69. The 2006 joint American Society of Clinical Oncology and Society of Surgical Oncology review assessing risk-reducing surgery in hereditary cancers recommended offering total colectomy plus ileorectal anastomosis or hemicolectomy as options to patients with Lynch syndrome and CRC, especially those who are younger.70. The Societies’ review also recommended offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch-anal anastomosis or anterior proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

The risk of endometrial cancer in MMR variant carriers has been estimated at 34% (95% CI, 17% to 60%) by age 70, and at 8% for ovarian cancer (95% CI, 2% to 39%) by age 70.71. Risks do not appear to appreciably increase until after age 40. Females with Lynch syndrome who choose risk-reducing surgery are encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. In a retrospective cohort study, Obermair et al (2010) found that hysterectomy improved survival among female colon cancer survivors with Lynch syndrome.72. This study estimated that, for every 100 women diagnosed with Lynch syndrome-associated CRC, about 23 would be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Surveillance in Lynch syndrome populations for ovarian cancer has not been demonstrated to be successful at improving survival.73.

**Section Summary: Lynch Syndrome and Colorectal Cancer Genetic Testing**
Direct evidence of clinical utility for genetic testing for Lynch syndrome is not available. Multiple studies have demonstrated clinical utility in testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed and did not follow recommended colonic surveillance. A positive genetic test for an MMR gene variant can also lead to changes in the management of other Lynch syndrome malignancies.
Genetic Testing for Juvenile Polyposis Syndrome and Peutz-Jeghers Syndrome

Clinical Context and Test Purpose

The purpose of genetic testing for Juvenile Polyposis syndrome (JPS) and Peutz–Jeghers syndrome (PJS) is:

- To confirm a diagnosis of JPS or PJS in individuals suspected of these disorders based on clinical features.
- To identify at-risk relatives of individuals with a confirmed diagnosis of JPS or PJS.

The following PICO was used to select literature to inform this review.

**Populations**

The relevant populations of interest are individuals with suspected JPS or PJS and individuals who are at-risk relatives of individuals suspected of or diagnosed with JPS or PJS.

**Interventions**

The relevant intervention is genetic testing for SMAD4 and BMPR1A (for JPS) and STK11 (for PJS). Commercial testing is available from numerous companies.

**Comparators**

The following practice is currently being used to make decisions about managing JPS and PJS: no genetic testing.

**Outcomes**

The potential beneficial outcomes of primary interest would be early detection of cancer and appropriate and timely interventional strategies (e.g., cancer screening, surgical intervention including polyp resection, gastrectomy, colectomy) to prolong life.

The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Genetic testing for SMAD4 and BMPR1A (for JPS) and STK11 (for PJS) may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual of having or developing JPS and PJS.

**Study Selection Criteria**

For the evaluation of the clinical validity of the genetic test, studies that met the following eligibility criterion were considered:

- Reported on the diagnostic yield of the test.

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Review of Evidence**

Table 1 summarizes clinical validity studies assessing genetic testing for JPS and PJS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calva-Cerqueira et al (2009)</td>
<td>Observational; 102 unrelated JPS probands analyzed all of whom met clinical criteria for JPS</td>
<td>SMAD4 and BMPR1A variants detected in 41% (42/102) JPS probands</td>
</tr>
<tr>
<td>Aretz et al (2007)</td>
<td>Observational; 80 unrelated patients (65 met clinical criteria for typical JPS; 15</td>
<td>SMAD4 and BMPR1A variants detected in 60% of typical JPS patients and none in</td>
</tr>
</tbody>
</table>
Study | Study Design and Population | Results
--- | --- | ---
Volikos et al (2006) | Observational; 76 clinically diagnosed with PJS | Detection rate of germline variants was about 80% (59/76)
Aretz et al (2005) | Observational; 71 patients (56 met clinical criteria for PJS; 12 presumed to have PJS) | STK11 variant detected in 52% (37/71)

JPS: juvenile polyposis syndrome; PJS: Peutz-Jeghers syndrome.

Clinical Usefulness
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified assessing the clinical utility of genetic testing for JPS and PJS.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of patients with suspected JPS and PJS has clinical utility:
- To make decisions about a preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis, segmental colectomy).

Genetic testing of individuals who are at-risk relatives of patients suspected of or diagnosed with JPS or PJS has clinical utility:
- If the individuals diagnosed with JPS and PJS are recommended for screening for JPS and PJS-associated cancers.
- If, in the absence of genetic testing, the diagnosis of JPS and PJS in at-risk relatives of patients can only be established by colonoscopy and subsequent histologic examination of excised polyps, which is burdensome.
- If negative test results in prompt release from an intensified screening program, thereby reducing an emotional burden.

A systematic review of 20 cohort studies with a total of 1644 patients with PJS was published by Lier et al (2010). A total of 349 patients developed 384 malignancies at an average age of 42 years. The lifetime risk for any cancer varied between 37% and 93% with relative risks (RRs) ranging from 9.9 to 18 versus the general population.

Section Summary: Genetic Testing for Juvenile Polyposis Syndrome and Peutz-Jeghers Syndrome
The likelihood of detecting a pathogenic variant is highly dependent on the presence of clinical features and family history. Detection rates have been reported to be between 60% and 41% for JPS, and 52% and 80% for PJS. Direct evidence of the clinical utility for genetic testing of JPS or PJS is not available. Genetic testing of patients with suspected JPS or PJS or individuals who are at-risk relatives of patients suspected of or diagnosed with a polyposis syndrome or PJS may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from an intensified screening program resulting in psychological relief, and improving health outcomes by identifying...
currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy.

**Supplemental Information**
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies and 3 academic medical centers while this policy was under review in 2009. In general, those providing input agreed with the overall approach described in this policy.

**Practice Guidelines and Position Statements**
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

**National Comprehensive Cancer Network**
The NCCN guidelines on genetic/familial high-risk assessment of colorectal cancer syndromes (v1.2023) are summarized in Table 2.

### Table 2. Criteria for Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer

#### Known LS pathogenic variant in the family

An individual with a LS-related cancer and any of the following:

- Diagnosed <50 y
- Another synchronous or metachronous LS-related cancer regardless of age
- 1 first-degree or second-degree relative with LS-related cancer diagnosed <50 y
- ≥2 first-degree or second-degree relatives with LS-related cancers regardless of age

#### Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age

#### Family history (on the same side of the family) of any of the following:

- ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 y
- ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer
- ≥2 first-degree or second-degree relatives with LS-related cancer, including ≥1 diagnosed <50 y
- ≥3 first-degree or second-degree relatives with LS-related cancers regardless of age

An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM5, MMRpro, MMRpredict)

- Individuals with a personal history of CRC and/or endometrial cancer with a PREMM5 score of ≥2.5% should be considered for MGPT.
- For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM5 score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.

CRC: colorectal cancer; IHC: immunohistochemistry; LS: Lynch syndrome; MGPT: multi-gene panel testing; MMR: mismatch repair; MSI: microsatellite instability; NGS: next generation sequencing; PCR: polymerase chain
reaction.

a LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, urethelial, brain (usually glioblastoma), biliary tract, and small intestinal cancers, as well as sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

b The NCCN recommends tumor screening for MMR deficiency for all CRC and endometrial cancers regardless of age at diagnosis. Tumor screening for CRCs for MMR deficiency for purposes of screening for LS is not required if MGPT is chosen as the strategy for screening for LS, but may still be required for CRC therapy selection. Consider tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreas, biliary tract, brain, bladder, urethelial, and adrenocortical cancers regardless of age at diagnosis. Direct referral for germline testing to rule out LS may be preferred in patients with a strong family history or if diagnosed prior to age 50 y, MSI-H, or loss of MMR protein expression. For patients aged ≥50 at CRC diagnosis, the panel has also recommended to consider germline MGPT evaluation for LS and other hereditary cancer syndromes.

Genetic Testing Recommendations for Lynch Syndrome

Screening of the tumor for defective DNA mismatch repair (MMR) using immunohistochemistry (IHC) and/or microsatellite instability (MSI) is used to identify which patients should undergo mutation testing for Lynch syndrome. The NCCN guidelines also indicate that BRAF V600E testing or MLH1 promoter methylation testing may be used when MLH1 is not expressed in the tumor on IHC analysis to exclude a diagnosis of Lynch syndrome.

The NCCN guidelines for colon cancer (v2.2023) recommend that all newly diagnosed patients with colon cancer be tested for MMR or MSI.

The NCCN guidelines for uterine neoplasm (v2.2023) also recommend universal screening for MMR genes (MSI testing if results are equivocal). Additionally, the NCCN guidelines recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years of age.

The NCCN guidelines for genetic/familial high-risk assessment: colorectal (v1.2023) recommend genetic testing for at-risk family members of patients with positive variants in MLH1, MSH2, MSH6, PMS2, and EPCAM. These guidelines also address familial adenomatous polyposis (classical and attenuated) and MUTYH-associated polyposis and are consistent with the information provided in this evidence review.

Surveillance Recommendations for Lynch Syndrome

The NCCN guidelines for colon cancer (v2.2023) and for colorectal cancer (CRC) screening (v1.2023) recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year postsurgery and, if normal, again in 3 years, then every 5 years based on findings.

The NCCN guidelines on genetic/familial high-risk assessment for CRC indicate for MLH1, MSH2, and EPCAM variant carriers that surveillance with colonoscopy should begin "at age 20 to 25 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years." MSH6 and PMS2 variant carriers should begin surveillance with colonoscopy "at age 30 to 35 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 30 years and repeat every 1 to 3 years".

Peutz-Jeghers Syndrome and Juvenile Polyposis Syndrome

There are limited data on the efficacy of various screening modalities in juvenile polyposis syndrome (JPS) and Peutz-Jeghers syndrome (PJS). The NCCN cancer risk and surveillance 2 category 2A recommendations for these indications are summarized in Tables 3 and 4.
### Table 3. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome

<table>
<thead>
<tr>
<th>Site</th>
<th>Lifetime Risk, %</th>
<th>Screening Procedure and Interval</th>
<th>Approximate Initiation Age, y</th>
</tr>
</thead>
</table>
| Breast                       | 32 to 54         | • Mammogram and breast MRI annually  
• Clinical breast exam every 6 mo | 30 y                          |
| Colon                        | 39               | Colonoscopy every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology | 18 y                          |
| Stomach                      | 29               | Upper endoscopy every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology | 18 y                          |
| Small intestine              | 13               | Small bowel visualization (CT or MRI enterography or video capsule endoscopy) every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology | 18 y                          |
| Pancreas                     | 11 to 36         | • Pelvic examination and Pap smear annually  
• Consider total hysterectomy (including uterus and cervix) once completed with childbearing | 30 to 35 y<sup>a</sup> |
| Cervix (typically minimal deviation adenocarcinoma) | ≥10   | • Pelvic examination and Pap smear annually  
• Consider total hysterectomy (including uterus and cervix) once completed with childbearing | 18 to 20 y |
| Uterus                       | 9                | • Annual pelvic examination with endometrial biopsy if abnormal bleeding | 18 to 20 y |
| Ovary (sex cord tumor with annular tubules) | ≥20   | • Annual pelvic examination with annual pelvic ultrasound | 18 to 20 y |
| Lung                         | 7 to 17          | • Provide education about symptoms and smoking cessation  
• No other specific recommendations have been made |               |
| Testes (Sertoli cell tumors) | 9                | • Annual testicular exam and observation for feminizing changes | Continued from pediatric screening |

CT: computed tomography; EUS: endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging.<br><br><sup>a</sup> Based on clinical judgment, early initiation age may be considered, such as 10 y younger than the earliest age of onset in the family.

### Table 4. Pediatric and Adult Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome

<table>
<thead>
<tr>
<th>Site</th>
<th>Lifetime Risk, % for SMAD4/BMPR1A variants</th>
<th>Screening Procedure and Interval</th>
<th>Approximate Initiation Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>up to 50</td>
<td>Colonoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18 y</td>
</tr>
<tr>
<td>Stomach</td>
<td>up to 21, especially if multiple gastric polyps present</td>
<td>Upper endoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>18 y</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Rare, undefined</td>
<td>No recommendations made</td>
<td></td>
</tr>
<tr>
<td>HHT</td>
<td>22</td>
<td>In individuals with SMAD4 variants, screen for vascular lesions associated with HHT</td>
<td>At time of diagnosis</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on clinical judgment, early initiation age may be considered, such as 10 y younger than the earliest age of onset in the family.
HHT: hereditary hemorrhagic telangectasia;
\(^a\) If polyp burden or polyp-related symptoms (i.e., anemia) cannot be controlled endoscopically or prevent optimal surveillance for cancer, consideration should be given to gastrectomy and/or colectomy.
\(^b\) While SMAD4 pathogenic variant carriers often have severe upper gastrointestinal tract involvement, BMPR1A pathogenic variant carriers may have a less severe upper gastrointestinal tract phenotype and may merit lengthened surveillance intervals in the absence of polyps. Gastric cancer risk for BMPR1A pathogenic variant carriers may be lower than for SMAD4 pathogenic variant carriers.

**American College of Gastroenterology**

The American College of Gastroenterology (2015) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.\(^{21}\)

For Lynch syndrome, the College recommended:

“All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency. Analysis may be done by immunohistochemical testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation.

Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF variant or hypermethylation of MLH1), a known family variant associated with LS [Lynch syndrome], or a risk of \(\geq 5\%\) chance of LS based on risk prediction models should undergo genetic evaluation for LS.\(^78\)

Genetic testing of patients with suspected LS should include germline variant genetic testing for the MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes or the altered gene(s) indicated by IHC testing.”

For adenomatous polyposis syndromes, the College recommended:

“**Familial adenomatous polyposis (FAP)/MUTYH-associated polyposis/attenuated polyposis**

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, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, 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 variant analysis.”

For juvenile polyposis syndrome, the College recommended:

“Genetic evaluation of a patient with possible JPS [juvenile polyposis syndrome] should include testing for SMAD4 and BMPR1A mutations”

“Surveillance of the gastrointestinal (GI) tract in affected or at-risk JPS patients should include screening for colon, stomach, and small bowel cancers (strong recommendation, very low quality of evidence).

Colectomy and ileorectal anastomosis or proctocolectomy and ileal pouch–anal anastomosis is indicated for polyp-related symptoms, or when the polyps cannot be managed endoscopically (strong recommendation, low quality of evidence).

Cardiovascular examination for and evaluation for hereditary hemorrhagic telangiectasia should be considered for SMAD4 mutation carriers (conditional recommendation, very low quality of evidence).”
For Peutz-Jeghers syndrome, the College recommended:

“Genetic evaluation of a patient with possible PJS [Peutz-Jeghers syndrome] should include testing for STK11 mutations.”

“Surveillance in affected or at-risk PJS patients should include monitoring for colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix, and testes cancers. Risk for lung cancer is increased, but no specific screening has been recommended. It would seem wise to consider annual chest radiograph or chest computed tomography (CT) in smokers (conditional recommendation, low quality of evidence).”

American Society of Clinical Oncology and Society of Surgical Oncology
The American Society of Clinical Oncology (2015) concluded the European Society for Medical Oncology clinical guidelines published in 2013 were based on the most relevant scientific evidence and therefore endorsed them with minor qualifying statements (in bold italics).79 The recommendations as related to genetic testing hereditary CRC syndromes are summarized below:

- If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.

- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1).

- Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis.

- Patients with multiple colorectal adenomas should be considered for full germline genetic testing of APC and/or MUTYH.

- Germline testing of MUTYH can be initiated by screening for the most common mutations (G396D, Y179C) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered.”

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for genetic testing of Lynch syndrome and other inherited colon cancer syndromes have been identified.

Medicare National Coverage
Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (i.e., clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. The Centers for Medicare & Medicaid Services recognizes Lynch syndrome as “an autosomal dominant syndrome that accounts for about 3% to 5% of colorectal cancer cases. [Lynch] syndrome variants occur in the following genes: hMLH1, hMSH2, hMSH6, PMS2, and EPCAM.” The Centers for Medicare & Medicaid Services also recognize familial adenomatous polyposis and MUTYH-associated polyposis syndromes and their associated variants.
Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02494791</td>
<td>Universal Screening for Lynch Syndrome in Women With Endometrial and Non-Serous Ovarian Cancer</td>
<td>886</td>
<td>July 2025</td>
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<tr>
<td>NCT04494945</td>
<td>Approaches to Identify and Care for Individuals With Inherited Cancer Syndromes</td>
<td>27500</td>
<td>Jun 2030</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01850654</td>
<td>Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome</td>
<td>3470</td>
<td>Jan 2018 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Laboratory invoice/order indicating specific test(s)/panel(s) and associated procedure codes
  - Personal and/or family history of cancer (if applicable) including: family relationship, cancer site(s), age at diagnosis
  - Preliminary diagnosis and prognosis
  - Specific test(s) requested and clinical reason/justification for testing
  - Treatment plan
  - Genetic counseling/professional results (if available)
  - Laboratory and/or Pathology report(s) (e.g., APC gene mutations, MSH2, MMR mutations, tumor MSI status)
  - Name of the test being requested or the Concert Genetics GTU identifier

The Concert Genetics GTU can be found at https://app.concertgenetics.com

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.
<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT*</td>
<td>0101U</td>
<td>Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only)]</td>
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<td>0130U</td>
<td>Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)</td>
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<td>0157U</td>
<td>APC (APC regulator of WNT signaling pathway) (e.g., familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)</td>
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<td>MLH1 (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)</td>
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<td>MSH6 (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)</td>
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<td>0161U</td>
<td>PMS2 (PMS1 homolog 2, mismatch repair system component) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)</td>
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<tr>
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<td>0162U</td>
<td>Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)</td>
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<td>0238U</td>
<td>Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions</td>
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<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
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<td>81202</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
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<tr>
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<td>81203</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81210</td>
<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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<td></td>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
</tr>
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<td></td>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
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<tr>
<td>---------------------------</td>
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<tr>
<td>Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes</td>
<td>81293</td>
<td><strong>MLH1</strong> (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td><strong>MLH1</strong> (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td><strong>MSH2</strong> (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td><strong>MSH2</strong> (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td><strong>MSH2</strong> (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
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<td><strong>MSH6</strong> (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td></td>
<td>81299</td>
<td><strong>MSH6</strong> (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<tr>
<td></td>
<td>81300</td>
<td><strong>MSH6</strong> (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81301</td>
<td>Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
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<td>81317</td>
<td><strong>PMS2</strong> (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81318</td>
<td><strong>PMS2</strong> (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<td><strong>PMS2</strong> (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td></td>
<td>81401</td>
<td>Molecular Pathology Procedure Level 2</td>
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<td></td>
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<td>Molecular Pathology Procedure Level 4</td>
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<td>Molecular Pathology Procedure Level 7</td>
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<td>Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including <strong>APC</strong>, <strong>BMPR1A</strong>, <strong>CDH1</strong>, <strong>MLH1</strong>, <strong>MSH2</strong>, <strong>MSH6</strong>, <strong>MUTYH</strong>, <strong>PTEN</strong>, <strong>SMAD4</strong>, and <strong>STK11</strong></td>
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<td>81436</td>
<td>Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including <strong>MLH1</strong>, <strong>MSH2</strong>, <strong>EPCAM</strong>, <strong>SMAD4</strong>, and <strong>STK11</strong></td>
</tr>
<tr>
<td></td>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
</tr>
</tbody>
</table>

**HCPCS** None
Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<td>05/01/2020</td>
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<td>Annual review. Policy statement, guidelines and literature review updated.</td>
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<td>12/01/2021</td>
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<td>12/01/2022</td>
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<td>12/01/2023</td>
<td>Policy statement, guidelines and literature review updated.</td>
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</table>

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member’s illness, injury, or disease.
Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.
Appendix A

<table>
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<tr>
<th>POLICY STATEMENT</th>
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**Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes 2.04.08**

**Policy Statement:**

**Note:** Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

**APC Testing**

I. Genetic testing of the APC gene may be considered **medically necessary** for a patient with any of the following:
   A. At-risk relatives (first or second degree) with familial adenomatous polyposis (FAP) or a known APC variant
   B. Personal history of 20 or more adenomas
   C. Personal history of between 10 to 20 polyps and 1 or more of the following:
      1. First or second degree relative with more than 20 polyps
      2. Other high-risk features as defined by a personal history of desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal or bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE)
   D. When included as part of an approved small genetic panel

II. Genetic testing for APC gene variants is considered **not medically necessary** for colorectal cancer (CRC) patients with classical FAP for confirmation of the FAP diagnosis.

**Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes 2.04.08**

**Policy Statement:**

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I. Genetic testing of the APC gene may be considered **medically necessary** for an individual with any of the following:
   A. At-risk relatives (first or second degree) with familial adenomatous polyposis (FAP) and/or a known APC variant
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   D. When included as part of an approved small genetic panel

II. Genetic testing for APC gene variants is considered **investigational** for colorectal cancer (CRC) **individuals** with classical FAP for confirmation of the FAP diagnosis.
### POLICY STATEMENT

#### III. Testing for germline *APC* gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

**MUTYH** Testing  
IV. Genetic testing of the **MUTYH** gene may be considered **medically necessary** for a patient with **any** of the following:  
   A. At-risk relatives (first or second degree) with a known MUTYH gene variant (single site analysis only)  
   B. A negative result for APC gene variants (when the criteria for approval of APC testing was met)  
   C. When included as part of an approved small genetic panel

#### V. Testing for germline **MUTYH** gene variants for inherited CRC syndromes is considered **investigational** in all other situations.

**MisMatch Repair (MMR) Gene and EPCAM Testing**

VI. Genetic testing for Lynch Syndrome (LS), also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), **MMR** genes (*MLH1, MSH2, MSH6, PMS2*); both initial sequencing and for deletions and duplications) and the EPCAM gene may be considered **medically necessary** for a patient with **any** of the following:  
   A. Family history of a known LS mutation (Variant single site analysis only)  
   B. Personal or family history of colorectal or endometrial cancer diagnosed before 50 years  
   C. Patients with CRC or endometrial cancer with tumor testing suggesting germline MMR deficiency (by microsatellite instability-MSI, or loss of mismatch repair protein expression by immunohistochemical-IHC- analysis) or meeting clinical criteria for Lynch syndrome  
   D. Personal or family history of at least 1 person with colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-related tumor in the same person  
   E. Personal (or family history of at least 2 people) with LS-related tumors and at least 1 diagnosed before 50 years of age

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   B. Personal or family history of colorectal or endometrial cancer diagnosed before 50 years  
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   E. Personal (or family history of at least 2 people) with LS-related tumors and at least 1 diagnosed before 50 years of age
### POLICY STATEMENT

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| **F.** Personal or family history of at least 3 people with **LS-related tumors**, regardless of age  
**G.** A 5% or more risk of having an MMR gene mutation based on predictive models (e.g., PREMM5, MMRpro, MMRpred) as documented in the medical record (See policy guidelines for calculators)  
**H.** No diagnosis of colorectal cancer (CRC) but with a **family history** meeting the Amsterdam criteria, when no affected family members have been tested for MMR variants (See policy guidelines; Revised Bethesda criteria are included in the above criteria)  
**I.** When included as part of an approved small genetic **panel** | **F.** Personal or family history of at least 3 people with **LS-related tumors**, regardless of age  
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**I.** When included as part of an approved small genetic **panel** |
| VII. Testing for germline MMR gene variants for inherited CRC syndromes is considered **investigational** in all other situations. | VII. Testing for germline MMR gene variants for inherited CRC syndromes is considered **investigational** in all other situations. |
| VIII. Testing for germline **EPCAM** gene variants for inherited CRC syndromes is considered **investigational** in all other situations. | VIII. Testing for germline **EPCAM** gene variants for inherited CRC syndromes is considered **investigational** in all other situations. |
| **SMAD4 and BMPR1A Testing**  
**IX.** Genetic testing of **SMAD4** and **BMPR1A** genes may be considered **medically necessary** when any of the following:  
**A.** Patient with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:  
1. At least 3 to 5 juvenile polyps in the colon  
2. Multiple juvenile polyps found throughout in other parts of the gastrointestinal tract  
3. Any number of juvenile polyps with a known **family history** of juvenile polyps  
**B.** At-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome  
**C.** When included as part of an approved small genetic **panel** | **SMAD4 and BMPR1A Testing**  
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**A.** An individual with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:  
1. At least 3 to 5 juvenile polyps in the colon  
2. Multiple juvenile polyps found throughout in other parts of the gastrointestinal tract  
3. Any number of juvenile polyps in a person with a known **family history** of juvenile polyps  
**B.** At-risk relative of an individual suspected of or diagnosed with juvenile polyposis syndrome  
**C.** When included as part of an approved small genetic **panel** |
<p>| X. Testing for germline <strong>SMAD4</strong> and <strong>BMPR1A</strong> gene variants for inherited CRC syndromes is considered <strong>investigational</strong> in all other situations. | X. Testing for germline <strong>SMAD4</strong> and <strong>BMPR1A</strong> gene variants for inherited CRC syndromes is considered <strong>investigational</strong> in all other situations. |</p>
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<tr>
<td><strong>STK11 Testing</strong></td>
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<tr>
<td>XI. Genetic testing for STK11 gene variants may be considered medically necessary in any of the following:</td>
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<tr>
<td>A. Patient with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:</td>
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<tr>
<td>1. Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the gastrointestinal tract</td>
</tr>
<tr>
<td>2. Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers</td>
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<tr>
<td>C. When included as part of an approved small genetic panel</td>
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<tr>
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<th>Panel Testing</th>
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<td>XIII. Limited genetic panels (including at a minimum APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, SMAD4, BMPRIA, and STK11 billed as CPT 81435) may be considered medically necessary as an alternative to serial testing of individual genes when criteria are met for any genetic testing of hereditary colorectal cancer, as indicated by one or more of the following:</td>
<td>XIII. Limited genetic panels (including at a minimum APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, SMAD4, BMPRIA, and STK11 billed as CPT 81435) may be considered medically necessary as an alternative to serial testing of individual genes when criteria are met for any genetic testing of hereditary colorectal cancer, as indicated by one or more of the following:</td>
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<td>B. Personal history of between 10 to 20 polyps and one of the following:</td>
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<td>2. Other high-risk features as defined by a personal history of desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal or bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE)</td>
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<td>C. Family history of a known LS mutation</td>
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<td>D.</td>
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XVI. The following are considered **investigational**:  
A. Large multi-gene panels including multiple genes that are not highly associated with hereditary colorectal cancer  
B. Genetic testing of all other genes for an inherited CRC syndrome  

XVII. The following are considered **investigational**:  
A. Large multi-gene panels including multiple genes that are not highly associated with hereditary colorectal cancer  
B. Genetic testing of all other genes for an inherited CRC syndrome