

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES
POLICY NUMBER	MP 5.013

CLINICAL BENEFIT	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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I. POLICY

APC Testing

Genetic testing for *APC* gene variants may be considered **medically necessary** in the following individuals:

- At-risk relatives (see Policy Guidelines section) of individuals with familial adenomatous polyposis (FAP) and/or a known *APC* variant; **or**
- Individuals with a differential diagnosis of attenuated FAP vs *MUTYH*-associated polyposis (MAP) vs Lynch syndrome. Whether testing begins with *APC* variants or screening for mismatch repair (MMR) variants depends on clinical presentation.

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

Testing for germline *APC* gene variants for inherited CRC syndromes is considered **investigational** in all other situations as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

MUTYH Testing

Genetic testing for *MUTYH* gene variants may be considered **medically necessary** in the following individuals:

- Individuals with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome and a negative result for *APC* gene variants. A family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

Testing for germline *MUTYH* gene variants for inherited CRC syndromes is considered **investigational** in all other situations as there is insufficient evidence to support

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a general conclusion concerning the health outcomes or benefits associated with this procedure.

MMR GENE Testing

Genetic testing for MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) may be considered **medically necessary** in the following patients:

- Individuals with CRC with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome (see Policy Guidelines section).
- Individuals with endometrial cancer with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome (see Policy Guidelines section).
- At-risk relatives (see Policy Guidelines section) of individuals with Lynch syndrome with a known pathogenic/likely pathogenic MMR gene variant.
 - Individuals with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. Whether testing begins with *APC* variants or screening for MMR genes depends on clinical presentation.
 - Individuals without CRC but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model (e.g., MMRpro, PREMM5 or MMRpredict), when no affected family members have been tested for MMR variants.

Testing for germline MMR gene variants for inherited CRC syndromes is considered **investigational** in all other situations as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

EPCAM Testing

Genetic testing for *EPCAM* gene variants may be considered **medically necessary** when any one of the following 3 major criteria (solid bullets) is met:

- Individuals with CRC, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when:
 - Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for a *MSH2* germline variant; or
 - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in *MSH2*, *MLH1*, *PMS2*, and *MSH6*; or
- At-risk relatives (see Policy Guidelines section) of patients with Lynch syndrome with a known *EPCAM* variant; or
- Individuals without CRC but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model (e.g. MMRpro, PREMM5 or MMRpredict), when no affected family members have been tested for MMR variants, and when sequencing for MMR variants is negative.

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Testing for germline EPCAM gene variants for inherited CRC syndromes is considered **investigational** in all other situations as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

BRAF V600E or MLH1 promoter methylation

Somatic genetic testing for *BRAF* V600E or *MLH1* promoter methylation may be considered **medically necessary** to exclude a diagnosis of Lynch syndrome when the *MLH1* protein is not expressed in a CRC tumor on immunohistochemical analysis.

Testing for somatic *BRAF* V600E or *MLH1* promoter methylation to exclude a diagnosis of Lynch syndrome is considered **investigational** in all other situations as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

SMAD4 and BMPR1A Testing

Genetic testing for *SMAD4* and *BMPR1A* gene variants may be considered **medically necessary** when any one of the following major criteria (solid bullets) is met:

- Individuals with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
 - At least five (5) juvenile polyps in the colon
 - Multiple juvenile polyps in other parts of the gastrointestinal tract
 - Any number of juvenile polyps in a person with a known family history of juvenile polyps.
- At-risk relative of an individual suspected of or diagnosed with juvenile polyposis syndrome.

Testing for germline *SMAD4* and *BMPR1A* gene variants for inherited CRC syndromes is considered **investigational** in all other situations as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

STK11 Testing

Genetic testing for *STK11* gene variants may be considered **medically necessary** when any one of the following major criteria (solid bullets) is met:

- Individuals with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any two (2) of the following:
 - Presence of two (2) or more histologically confirmed Peutz-Jeghers polyps of the gastrointestinal tract
 - Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
 - Family history of Peutz-Jeghers syndrome
- At-risk relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome.

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Testing for germline STK11 gene variants for inherited CRC syndromes is considered **investigational** in all other situations as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Other Variants

Genetic testing for all other gene variants for Lynch syndrome or CRC is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

GENETIC COUNSELING

Pre- and post-test genetic counseling may be considered **medically necessary** as an adjunct to the genetic testing itself.

POLICY GUIDELINES

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-degree relatives. However, some judgment must be allowed, e.g., in the case of a small family pedigree, when extended family members may need to be included in the testing strategy. A family history might include at least two (2) second-degree relatives with a Lynch syndrome-related cancer, including at least one (1) diagnosed before 50 years of age, or at least three (3) second-degree relatives with a Lynch syndrome-related cancer, regardless of age.

Targeted Familial Variant Testing

It is recommended that, when possible, initial genetic testing for familial adenomatous polyposis 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.

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 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.

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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.

When indicated, genetic sequencing for MMR gene variants should begin with *MLH1* and *MSH2* genes, unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications; when MMR gene variants are expected based on IHC or MSI studies, but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

The Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent criteria for defining families at high-risk for Lynch syndrome (Vasen et al, 1999):

- Three (3) or more relatives with an associated cancer (CRC, or cancer of the endometrium, small intestine, ureter, or renal pelvis);
- One (1) should be a first-degree relative of the other two (2);
- Two (2) or more successive generations affected;
- One (1) or more relatives diagnosed before the age of 50 years;
- Familial adenomatous polyposis 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 two (2) CRCs in first-degree relatives if at least two (2) generations have the cancer and at least one (1) case of CRC was diagnosed by the age of 55 years;
 - OR: In families with two (2) first-degree relatives affected by CRC, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

The Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families (Umar et al, 2004). The Bethesda guidelines are also considered more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

- CRC diagnosed in a patient who is less than 50 years old;
- Presence of synchronous or metachronous CRC or other HNPCC-associated tumors,* regardless of age;
- CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old;
- CRC diagnosed in one (1) or more first-degree relatives with a Lynch syndrome-associated tumor, with one of the cancers being diagnosed at younger than 50 years of age;
- CRC diagnosed in two (2) or more first or second-degree relatives with HNPCC-related tumors,* regardless of age.

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* HNPCC-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.

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.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease

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Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

III. DESCRIPTION/BACKGROUND

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Hereditary Colorectal Cancers

Currently, two (2) types of hereditary colorectal cancers are well-defined: familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer [CRC]). Lynch syndrome has been implicated in some endometrial cancers as well.

FAP and Associated Variants

FAP 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 go on to develop CRC. Mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP 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. FAP associated with these collective extra-intestinal manifestations is sometimes referred to

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as Gardner syndrome. FAP 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 later in life (at an average age of 50 to 55 years) but lifetime risk of CRC remains high (~70% by age 80 years). The risk of extra-intestinal 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). MAP occurs with a frequency approximately equal 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 among 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 vs MAP vs 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

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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. However the risk varies by genotype. It occurs as a result of germline variant 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. Also, variants in 3 additional genes (*MLH3*, *PMS1*, *EXO1*) have also been implicated with Lynch Syndrome. Notably, in individuals meeting the various clinical criteria for Lynch syndrome, 50% 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 one 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 three (3) testing strategies.

1. 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.
2. IHC testing (phenotype): Individuals with negative staining would proceed to genetic testing for *MLH1*, *MSH2*, *MSH6*, and *PMS2*.
3. 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 with 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 detect MSI (Bethesda markers). MSI detection in 2 of these markers is considered a positive result or “high probability of MSI”.

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

BRAF testing is an optional screening method that may be used in conjunction with IHC testing for *MLH1* to improve efficiency. A 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. MSI testing performance depends on the specific MMR variant. MSI screening 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

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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. IHC screening has 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 a 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. 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.

Novel deletions have been reported to affect the expression of the *MSH2* gene in the absence of a *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, results 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 a *MSH2* variant prevents *MSH2* gene expression.

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 one 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. 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 non-expression, 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.

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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 criteria¹⁹ (low sensitivity but high specificity), Bethesda guidelines (better sensitivity but poorer specificity) and risk prediction models (e.g., MMRpro; PREMM5; MMRpredict). 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 patients with CRC 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 vs attenuated FAP vs 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 and benefits 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 juvenile polyposis 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 colorectal 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 colorectal 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

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diagnosis of 58 years. JPS 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 one 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 characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and non-gastrointestinal 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 colon and rectum, followed by breast, stomach, small bowel, and pancreas. The estimated lifetime risk of gastrointestinal cancer ranges from 38% to 66%. Lifetime cancer risk stratified by organ site is colon and rectum (39%), stomach (29%), small bowel (13%), and pancreas (11%-36%).

Diagnosis

A clinical diagnosis of PJS is made if an individual meets two or more of the following criteria: presence two 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. 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.

Regulatory Status

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. Genetic tests reviewed in this

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evidence review are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence

For individuals who are suspected of attenuated FAP, MAP, and Lynch syndrome who receive genetic testing for *APC*, or are at-risk relatives of patients with FAP who receive genetic testing for *MUTYH* after a negative *APC* test result, the evidence includes a TEC Assessment. The relevant outcomes are overall survival (OS), disease-specific survival, and test accuracy and validity. For patients with an *APC* variant, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. A related familial polyposis syndrome, MAP syndrome, is associated with variants in the *MUTYH* gene. Testing for this genetic variant is necessary when the differential diagnosis includes both FAP and MAP because distinguishing between the two leads to different management strategies. Depending on the presentation, Lynch syndrome may be part of the same differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, or (2) have colon cancer, or (3) have endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, or (4) are at-risk relatives of patients with Lynch syndrome, or (5) are without colon cancer but with a family history meeting Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model, who receive genetic testing for MMR genes, the evidence includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in CRC. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. A chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known variant in an MMR gene, 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 recommended colonic surveillance. A positive genetic test for an MMR variant can also lead to changes in the management of other Lynch syndrome malignancies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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For individuals who warrant Lynch testing, screen negative on MMR testing, but positive for microsatellite instability and lack MSH2 protein expression who receive genetic testing for *EPCAM* variants, the evidence includes variant prevalence studies and case series. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown an association between *EPCAM* variants and Lynch-like disease in families, and the cumulative risk for CRC is similar to carriers of an *MSH2* variant. Identification of an *EPCAM* variant could lead to changes in management that improve health outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CRC in whom MLH1 protein is not expressed on immunohistochemical analysis who receive genetic testing for *BRAF* V600E or *MLH1* promoter methylation, the evidence includes case series. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between *BRAF* V600E variant and *MLH1* promoter methylation with sporadic CRC. Therefore, this type of testing could eliminate the need for further genetic testing or counseling for Lynch syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who (1) are suspected of JPS or PJS or (2) are at-risk relatives of patients suspected of or diagnosed with JPS or PJS who receive genetic testing for *SMAD4*, *BMPR1A*, or *STK11* genes, respectively, the evidence includes multiple observational studies. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between *SMAD4* and *BMPR1A* and *STK11* variants with JPS and PJS, respectively. Direct evidence of clinical utility for genetic testing of a JPS or PJS is not available. Genetic testing may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

V. DEFINITIONS

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ADENOMA is a benign tumor made of epithelial cells, usually arranged like a gland.

ADENOCARCINOMA is a malignant tumor arising from a glandular organ.

FAMILIAL ADENOMATOUS POLYPOSIS is an inherited disorder characterized by the development of myriad polyps in the colon beginning in late adolescence or early adulthood. Untreated, the condition leads to colon cancer.

FIRST-DEGREE RELATIVE refers to parent, offspring, and siblings.

LYNCH SYNDROME is a hereditary predisposition to nonpolyposis colorectal cancer and other solid tumors.

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METACHRONOUS means not synchronous; multiple separate occurrences, such as multiple primary cancers developing at intervals.

MUTATION refers to an unusual change in genetic material occurring spontaneously or by induction.

NONINVASIVE refers to a device or procedure that does not penetrate the skin or enter any orifice in the body.

OSTEOMA refers to a benign bony tumor.

PHENOTYPE is the expression of genes present in an individual. This may be directly observable (e.g., eye color) or apparent only with specific tests (e.g., blood type).

POLYPOSIS refers to the presence of numerous polyps.

SECOND DEGREE RELATIVE (i.e., grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling)

SYNCHRONOUS refers to occurring at the same time.

SCREENING refers to evaluating a patient for diseases such as cancer, heart disease, or substance abuse before they become clinically obvious.

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
0157U	0158U	0159U	0160U	0161U	0162U	0238U	0474U	81201

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Procedure Codes								
81202	81203	81210	81288	81292	81293	81294	81295	81296
81297	81298	81299	81300	81301	81317	81318	81319	81403
81435								

ICD-10-CM Diagnosis Code	Description
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
D01.0	Carcinoma in situ of colon
D01.1	Carcinoma in situ of rectosigmoid junction
D01.2	Carcinoma in situ of rectum
D01.3	Carcinoma in situ of anus and anal canal
D01.4	Carcinoma in situ of other and unspecified parts of intestine
D01.7	Carcinoma in situ of other specified digestive organs
D01.9	Carcinoma in situ of digestive organ, unspecified
D12.0	Benign neoplasm of cecum
D12.1	Benign neoplasm of appendix
D12.2	Benign neoplasm of ascending colon
D12.3	Benign neoplasm of transverse colon
D12.4	Benign neoplasm of descending colon
D12.5	Benign neoplasm of sigmoid colon
D12.6	Benign neoplasm of colon, unspecified
D12.7	Benign neoplasm of rectosigmoid junction

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ICD-10-CM Diagnosis Code	Description
D12.8	Benign neoplasm of rectum
D12.9	Benign neoplasm of anus and anal canal
D13.91	Familial adenomatous polyposis
D13.99	Benign neoplasm of ill-defined sites within the digestive system
K63.5	Polyp of colon
Z15.060	Genetic susceptibility to colorectal cancer
Z31.5	Encounter for genetic counseling
Z80.0	Family history of malignant neoplasm of digestive organs
Z83.72	Family history of familial adenomatous polyposis
Z85.030	Personal history of malignant carcinoid tumor of large intestine
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.040	Personal history of malignant carcinoid tumor of rectum
Z85.04	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z86.0100	Personal history of colon polyps, unspecified
Z86.0101	Personal history of adenomatous and serrated colon polyps
Z86.0102	Personal history of hyperplastic colon polyps
Z86.0109	Personal history of other colon polyps

VIII. REFERENCES

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MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES
POLICY NUMBER	MP 5.013

IX. POLICY HISTORY

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MP 5.013	11/18/2020 Administrative Update. Added new code 0238U.
	12/15/2021 Minor Review. Updates to JPS diagnosis criteria and MMR gene testing. Background, rationale references updated. Coding reviewed.
	12/16/2022 Consensus Review. No changes to policy statement. Updated background, references. No coding changes.
	10/01/2023 Administrative Update. New diagnosis codes D1391 and D1399 added to the policy from new code review.
	09/29/2023 Consensus Review. No changes to policy statement. References reviewed and updated. Coding reviewed.
	06/10/2024 Administrative Update. Added code 0474U. Effective 07/01/2024.
	08/19/2024 Administrative Update. Added ICD 10 codes effective 10/01/2024.
	12/10/2024 Administrative Update. Removed 81436 effective 01/01/2025
	12/13/2024 Administrative Update. Removed NCCN statement.
	01/13/2025 Consensus Review. Minor editorial updates to policy statement, no changes to intent. References updated. Removed code 0421U, otherwise no changes.
	05/15/2025 Consensus Review. No changes to policy statement.
	9/2/2025 Administrative Update. Added ICD 10 code Z15.060 effective 10/01/2025
	10/22/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/04/2026 Retirement Review. EviCore delegation.

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